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BRITISH MEDICAL JOURNAL

LONDON SATURDAY MAY 16 1953

EPIDEMIC HAEMORRHAGIC FEVER

40 CASES FROM KOREA

BY

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This paper is written from experience gained at the British Commonwealth General Hospital (Japan) in treating 40 cases of this disease during the eight-months period June, 1951, to January, 1952. A far greater number of cases occurring in members of the United Nations Forces have been treated by American hospitals in Korea and Japan, and therefore their figures, when published, will be of greater statistical significance than my own.

Historical

Available literature indicates that the disease was known to the Japanese during their occupation of Manchuria after 1939, and was called variously after the place names where it was endemic—Ehr-Tao-Kang disease, Sun-wu disease, and Songo fever—until the identity of the condition was realized, when the descriptive title "epidemic haemorrhagic fever" was coined.

By 1942 investigations into its aetiology resulted in the belief that the responsible agent was a virus transmitted by the bite of an infected mite *(Laelaps jettmari litzthum)*. Such mites were harboured by the field rodent *Apodemus agrarius*, which was as common in Manchuria as in Korea. The Japanese succeeded in producing fever in one monkey 19 days after a subcutaneous injection of 1 ml. of an emulsion of 203 mites collected from 40 *A. agrarius* rodents, and in producing fever, albuminuria, and the characteristic kidney lesion in a second monkey 12 days after its inoculation with the blood from the first.

The incidence of the disease was greatest in the months of May, June, October, and November, and was most prevalent among troops stationed on damp ground and near river banks. Those men who were often in close contact with pack animals also seemed to be prone to the infection. Epidemics varied in their severity and carried case mortalities of from 15 to 50%. The incubation period was estimated at two to three weeks, and ranged from one week to one month.

Incidence in Commonwealth Troops

The cases were scattered among 15 regiments and corps, the maximum number occurring in any one of these not exceeding four during any month from June, 1951, to January, 1952. Cross-infection was therefore improbable. There was, however, an apparent increase in morbidity during the autumn months, and fully half the cases arose during November, 1951.

All cases of the disease in these troops arose during service in Korea or not later than eight days after leaving that country. The endemic areas, chiefly bordering on the River Imjin, had previously been occupied by Chinese and North Korean troops with their pack animals; the vegetation along the river banks is believed to be most favourable for the *A. agrarius* rodent, though these are common throughout Korea. Our patients remembered the friendly habits of these "field mice," which were to be found in the straw insulating shields covering their trenches, and frequently venturing within. Some were tame enough to take food from the men's hands. One patient found one in his bedding a month before his disease began; he developed severe haemorrhages during the course of his illness and died.

Early Symptoms

Initial symptoms were commonly of sudden onset and were attributed by the sufferer to a "flu-like" cold. Chills, headache, anorexia, and nausea were noted by most patients on the first day; sore throat, vertigo, abdominal pain, and vomiting were initial symptoms noted by a few. The chronological order and severity of these symptoms were very variable: chills, 85%; headache, 74%; anorexia, 65%; abdominal pain, 44%; prostration, 30%; vomiting, 24%; sore throat, 17%; vertigo, 15%.

The chills recurred frequently and were accompanied by tremors, which were often remarked upon by the patient's friends before they were noted by him. Headache was absent in no less than 26%, and was often mild and limited to the retro-orbital regions; later it became severe in a few, and was then usually frontal. Vertigo and sufficient subjective loss of postural sensation to cause periodic stagger were present in a minority of cases on the first and second days; dizziness was more commonly described. Abdominal symptoms were early in less than half the cases if slight anorexia and nausea alone are not included. However, within three days pain in the right upper quadrant, with vomiting, frequently became severe, and an initial diagnosis of intestinal obstruction or infective hepatitis was often made. Sore throats and cough were seldom troublesome, and myalgia of back and limbs, though present in most, was rarely severe.

The majority of our cases did not report sick until the third day of illness, when their average temperature was 102.6° F. (39.2° C.).

The Febrile Period

Duration.—The period of fever noted in 34 cases averaged 5.5 days ; two cases had a three-day fever, five a four-day fever, seven a five-day fever, eleven a six-day fever, and nine remained febrile on or after the seventh day of the disease. As this duration was estimated from the first day of illness and these patients did not report sick and have their temperature noted until the second or third day, it is possible that the actual duration of fever was shorter in some owing to a brief afebrile prodromal period being included. It appears likely, however, that the discrepancy is slight, as 85% of our cases described chills on their first day's illness, and these presumably coincided with the onset of the febrile period.

Temperature Trends.—An accurate appreciation of the initial two days' fever could not be made owing to lack of temperature recordings over this period in most cases, indeed, only 13 cases reported sick on the second day. The latter showed a temperature of 100–105° F. (37.8–40.6° C.). If the temperature was below 103° F. (39.4° C.) its trend was to rise gradually to a peak of 104–105° F. (40–40.6° C.) on the third or fourth day and then to decline steadily, suddenly, or occasionally intermittently to normal over the next 48 hours. If the temperature on the second day was recorded as 104–105° F. (40–40.6° C.) this appears to have been the fastigium, and it then fell by crisis or by lysis over a similar period. Once the temperature returned to normal it seldom attained 99° F. (37.2° C.) thereafter, and no true relapses occurred.

The more severe haemorrhagic manifestations occurred as sequelae to a sustained fever or to one with a temperature of 104–105° F. (40–40.6° C.) at some time. During the febrile stage a relative bradycardia was commonest.

Symptoms and Signs

Gastro-intestinal

Discomfort and tenderness in the central abdomen, epigastrium, or right hypochondrium generally preceded the vomiting phase and continued after this had ceased. Described as colicky with a lingering dull ache, it was often so mild as to cause no complaint, or it was so severe as to require antispasmodics and opiates for its relief. There was a tendency for gaseous distension and constipation to accompany the complete anorexia, the distension being aggravated by hiccup.

Vomiting began 48–72 hours before the fever abated but at any time between the first and seventh days of illness ; it continued for an average period of 4.8 days, with extremes of 1 and 14 days, and was perhaps the most distressing and important sign that occurred during the febrile period. The vomiting appeared to cause greater exhaustion than shown by a case of diarrhoea with equivalent fluid losses. Severe diarrhoea was not an added feature, fortunately. Several of our patients vomited and retched every hour of the day and night for 48 hours or more : there appeared to be little change whether the stomach was given small amounts of semi-solid food or kept empty by continuous aspiration ; vomiting of small-gut contents containing bile and pancreatic juices still occurred, and we felt that in most cases 4–6 oz. (114–170 ml.) of fluid hourly by mouth gave the patient most comfort.

Urinary

Albuminuria began on the fourth to the sixth day of illness. It preceded the onset of vomiting in two cases, but in the remainder no albuminuria was found until vomiting had proceeded for two or more days. The two symptoms bore no relationship to each other in respect of severity : albuminuria always continued the longer, and was attributed to an acute nephritis owing to the presence of red cells and casts in the urine in all cases. Glomerular damage usually occurred first, as the specific gravity of the urine was high and microscopy showed many red cells ; granular and hyaline casts appeared later, with a steady lowering of specific gravity. The urine boiled solid in three cases. Oliguria lasted 2 to 14 days ; suppression to the degree of clinical anuria occurred in seven cases and lasted 1 to 10 days.

Chloride loss by vomiting was not compensated by the kidneys, and urinary chloride levels gave no indication of the resulting hypochloraemia, which was often severe and tended to enhance the nephritis and nitrogen retention.

Oedema was seldom notable, and was confined to the face, making this look bloated until diuresis occurred. Exceptionally, the conjunctivae appeared chemotic ; abdominal distension and loin pain were partially attributable to oedema of the abdominal viscera, particularly the perirenal tissues ; lethargy, apathy, sluggish tendon reflexes, and cerebral irritation accompanied by fits may have been due to oedema of the central nervous system combined with a relative chloride depletion.

Vascular

Vascular dilatation was chiefly noted in the face, which appeared sunburnt throughout the acute illness, and by inference from blood-pressure recordings. By the time the patient was admitted to hospital the blood pressure was generally normal or high and albuminuria had already begun, but readings taken before admission indicated that there had been a phase of hypotension preceding the onset of nephritis in nearly every case upon which a record had been kept. It was common for us to find that a patient admitted on the ninth or tenth day with a blood pressure of 150/120 had had a recorded pressure of 90/60 on the fifth or sixth day, and that for one or two days this hypotension accompanied the onset of albuminuria and defervescence. Thereafter a plateau rise of blood pressure usually occurred ; the hypertension continued throughout the nephritic stage and for several days into the convalescent period.

The most noteworthy vascular changes were those of capillary endothelial damage occurring throughout the body, manifested in all cases by petechial haemorrhages into the skin and visible mucous membranes, and in the most severe cases by overt haemorrhages from the respiratory, gastro-intestinal, and urinary tracts. As a rule these did not begin until the third to sixth day of illness, and continued until the tenth day. Injection of the conjunctivae and the appearance of a few petechiae in the sublingual mucosa were the only manifestations in mild cases ; in those more severely afflicted subconjunctival haemorrhages occurred, often visible over the peripheral sclera only after eversion of the eyelids. Thirteen of our cases showed such haemorrhages in one or both eyes, but in none did they assume the grosser form described, in which the whole sclera of both eyes appeared cherry red. Petechiae in the skin occurred in approximately half the cases, generally confined to the neck and axillary folds, more rarely over thorax, abdomen, and limbs.

Epistaxis was noted in 12 cases, in 2 of which it was severe. Haemoptysis is said to be a sign, but was absent in our cases. Haematuria sufficient to colour the urine was present in six cases and continued for several days ; in the majority, microscopic haematuria was noted on the day albuminuria was discovered. Haematemesis was noted in six cases but melaena in only one case.

The Blood

An initial leucopenia is said to be characteristic of the disease, but was noted in one case only, which showed a white-cell count of 3,000 per c.mm. on the third day ; however, no case had a white-cell count recorded before the third day. Leucocytosis was noted on or after the third

day in all other cases; however, there were as many cases showing a total count below 10,000 as above this figure on the third day. The peak leucocytosis of 10,000 to 64,000 was generally found on the sixth day, and on that day as many cases showed a count of 10,000 to 20,000 as showed a count of 20,000 to 64,000. The increase was greatest in the polymorph neutrophils, which showed a shift to the left; primitive cells of the myeloid series appeared in the peripheral blood in 14 cases. Red-cell counts were not performed routinely; haemoglobin estimations yielded high figures in the early part of the febrile period secondary to haemoconcentration, and they seldom became low except in the presence of frank haemorrhages. Thrombocytopenia, which is said to occur in the fastigium, was not noted, but insufficient counts were made to assess any change.

Those cases in which prothrombin times were estimated showed no appreciable increase. Clotting-times were normal and bleeding-times not increased in our earlier cases; routine examinations were not carried out in later cases, and little appreciable change has been reported by other workers. Clot-retraction time has been found to be prolonged during the fastigium.

Blood chlorides showed a decrease as early as the fifth day, and unless measures were taken to restore the deficiency they continued to decrease until convalescence was reached. In most cases in which vomiting ceased within three to four days, chloride by mouth could be given and retained, but in others it was given parenterally; chloride by either route was found to be rapidly excreted by the kidneys, and the deficiency could never be fully overcome.

Blood urea levels of 150–450 mg. per 100 ml. were recorded; the rise tended to continue for several days after vomiting had ceased and diuresis had begun.

Central Nervous System

Mental apathy and lethargy were common, and from the earliest days of the illness some patients felt muzzy-headed, failed to recognize friends, and lost memory for recent events; later, in those severely ill there was delirium, with a tendency to wander at night, to spit, shout, or swear in garbled fashion, and to be averse to any interference.

Blurred vision was noted by 15 patients, beginning in the first two-weeks period, and continuing for one to seven days; it was commonest during the period of oliguria, and usually disappeared after the onset of diuresis. Transient diplopia on the second and third days was noted by one patient. Mydriasis, apparently characteristic of the disease, was infrequently found, and the blurred vision could not be attributed to it; in one case, however, the pupils were at maximum diameter, and an associated sleeplessness and autonomic disturbance suggested a hypothalamic lesion.

Tendon reflexes were normal in 17 cases, brisk in 5, and sluggish in 2; in one case they could not be elicited on the third day but were remarkably brisk on the fifth.

Photophobia was noted by one patient only; he had Jacksonian fits on the tenth day and meningismus on the twelfth, when his C.S.F. was normal. Another patient had fits on the eighth day, when examination showed: blood pressure, 180/120; blood urea, 184 mg. per 100 ml.; blood chloride (as NaCl), 397 mg. per 100 ml. Fits recurred on the thirteenth and fourteenth days, to be apparently terminated by relief of a high C.S.F. pressure (230 mm. C.S.F.; cells 3 per c.mm.; protein 55 mg. per 100 ml., globulin not increased, sugar 50 mg. per 100 ml., chlorides 770 mg. per 100 ml.). A third patient had fits of epileptiform character on the twelfth and thirteenth days, starting after the onset of diuresis following anuria on the second day and macroscopic haematuria from the ninth day; these fits were probably occasioned by electrolyte imbalance and a high blood urea or by haemorrhages in the brain. In no case were any permanent changes recognized, and none of these patients admitted to a past epileptic history.

Convalescent Phase

It has been noted above that after defervescence, vomiting commonly continued for three to four days, haemorrhagic manifestations for four to five days, and albuminuria with cylinduria for a week or longer. The full effects of the infection thus seemed to arise paradoxically after the fever, and to be due to a combination of toxic effects from the infection itself upon certain capillaries, the kidneys, and stomach, and of resultant secondary biochemical changes, which often progressed towards exacerbation of the primary cause. Thus vomiting would be exacerbated by the uraemia following renal failure; and chloride loss from vomiting, with haemoconcentration from capillary transudation, would exacerbate renal failure.

The most permanent effects noted were those upon the kidney. Casts disappeared often by the end of the first week, and always by the end of the third week; such evidence of tubular damage was always followed by a failure of the kidney to concentrate urine for a considerably longer period, up to three months. This was not shown as a fixed urinary specific gravity: dilution of the urine below an S.G. of 1010 was always possible. The diuresis, which began generally between the eighth and eleventh days and continued for a week or more, was also usually followed by an apparent lack of the normal nocturnal inhibition of urinary secretion, and night and day urines became approximated in volume. These effects, it was suggested, might well have arisen from pituitary or hypothalamic disturbance, but experimentally they were not overcome in three cases which were given 1-ml. injections of posterior lobe extract after 18 hours' abstention from fluids; there was some lessening of nocturia but no increase in concentrating power of the renal tubules following this trial.

Continued low lumbar ache was persistent and a cause of complaint in about half our cases after all other symptoms had disappeared; it seemed to be spinal or ligamentous in origin, and was exacerbated by walking relatively short distances, so that a patient returning from the convalescent home at the sixth or seventh week after the onset of his disease would state that he could not keep up a walk for more than 10–15 minutes, as his backache then became severe.

Treatment

The earliest case of infection, diagnosed in retrospect, occurred in June, 1951, and was treated by Lieutenant Poole under the direction of Lieutenant-Colonel Mackay Dick. This patient had been ill for seven days and anuric for four days before admission to this hospital. Treatment along modern lines by intragastric drip of a Hammersmith cocktail mixture (400 g. glucose, 100 g. peanut oil, acacia q.s. to emulsify, water to 1 litre) was immediately started, the vomitus being filtered and returned to the stomach to prevent loss of electrolytes. Four days later, after an intake of 1 litre of this mixture daily, the patient excreted 7 oz. (200 ml.) urine; after seven days of this treatment there was natural micturition of 32 oz. (900 ml.) in 24 hours; after 12 days the treatment was stopped. Intravenously, one-fifth normal saline with 4% glucose was given after the kidneys had resumed some function, and this was later increased to one-half strength normal saline because blood and urinary chlorides were low. This case had been given aureomycin and penicillin at the advanced dressing station, where acute bronchitis had been noted; and procaine penicillin, 60,000 units twice daily, was given in hospital for nine days, the course being terminated on the appearance of a penicillin rash.

For later cases presenting anuria the same principles of treatment were followed—namely, limitation of fluid intake; conservation of electrolytes; and the supply of minimum daily energy requirements by a high-carbohydrate and high-fat diet in fluid form.

Chemotherapy was not given in uncomplicated cases, as no benefit was derived from the use of chloramphenicol, streptomycin, aureomycin, or penicillin in this disease.

Convalescent serum is stated to be of value if given intravenously during the early phase of infection. Three of our cases were treated with this rather later, and no appreciable benefit could then be attributed to it.

Sedation was often required for restlessness or delirium: paraldehyde by intramuscular injection sometimes exacerbated these conditions; parenteral barbiturates were found more effective, but were limited owing to their possible cumulative effects.

Hiccups often appeared intractable to any form of treatment, including the administration of oxygen and 5% CO_2, intramuscular magnesium sulphate 8% solution or ether, and sedatives.

Case 37

A lieutenant aged 28 was admitted on September 16, 1951. On September 9–10 he had led an artillery section on the south bank of the River Imjin, and ate little food and had no sleep. On the 11th he felt ill and shivered, retired to rest, and three hours later could not rise to micturate but filled a 2-pint (1-litre) pot with urine which looked red. Severe headache and vomiting started while he was on his way to the field ambulance, where a temperature of 105.6° F. (40.9° C.), pulse 84–104, and signs of bronchopneumonia were found. Penicillin and sulphadimidine courses were begun.

2nd day.—T. 103.4° F. (39.7° C.), signs of pneumonia extending.

3rd day.—T. 101–99° F. (38.3–37.2° C.), great mental depression, persistent hiccup.

4th day.—T. normal, bronchial breathing entire chest, few rales only at left lower lobe.

5th day.—Claimed not to have voided for several days. Catheterized, 3 oz. (85 ml.) dark urine, S.G. 1017, albumin 4 plus, frequent white and red blood cells.

6th day.—Circulatory failure on arrival at airport during evacuation to Japan, O_2 and intravenous glucose given. On admission to this hospital he complained of backache, headache, intense thirst, hiccups, suppression of urine, and vomiting of blood-stained mucus of three days' duration. T. 97° F. (36.1° C.), P. 105, R. 25, B.P. 115/70. Appeared very ill; conjunctival injection, dry tongue, mydriasis. No adenopathy. Heart and lungs normal. Slight abdominal distension and renal tenderness, no organ enlargement. Catheterized, 4 oz. (114 ml.) dark-yellow urine—acid, albumin 3 plus, no sugar; microscopical examination: W.B.C. and R.B.C. filled the field, no casts or crystals seen, numerous epithelial cells, cellulose test for sulphonamides positive, culture sterile. C.N.S. normal but for mental retardation. Blood urea 240 mg. per 100 ml., W.B.C. 21,000 (P. 74%, L. 14%, M. 12%). The diagnosis made was ? Weil's disease. Treatment: intragastric drip of Hammersmith cocktail, 3,000,000 units penicillin daily, chloramphenicol 3 g. followed by 0.5 g. six hourly.

8th day.—Very drowsy, but by this time had voided 68 oz. (1.9 litres) urine. Abdomen greatly distended, bowel sounds absent, intestinal obstruction considered present, and Miller-Abbott tube inserted following enema. B.P. 110/70, P. 110. Reflexes hypoactive in upper limbs and absent in lower limbs. Intravenous saline given slowly.

9th day.—Unable to tolerate tube, but abdomen less distended, green foul-smelling stools passed, no further vomiting. His respirations slowed to 10 a minute and oxygen and nikethamide given. B.P. 170/95. Urinary output 97 oz. (2.8 litres), containing scanty R.B.C., few W.B.C., no casts.

10th day.—Still drowsy. B.P. 150/75. Rales appeared at both lung bases and a mitral systolic murmur was evident. Blood urea, 265 mg. per 100 ml. Plasma proteins, 6.2 g. %; W.B.C. 14,600 (P. 83%, L. 14%, M. 2%, E. 1%); R.B.C., 2,100,000; Hb, 8 g.%. Blood transfusion of 2 pints (1.1 litres) fresh blood.

12th day.—Less drowsy, fewer hiccups. Serum chlorides, 590 mg. per 100 ml.; Hb 9 g.%; R.B.C. 2,500,000. Albuminuria continued in diminishing quantities; he was now able to take a low protein diet and an adequate quantity of fluid orally. Casts were not found in the urine until September 28 (18th day).

19th day.—A second blood transfusion of 1 pint (570 ml.) whole blood was given with improvement of his anaemia. Thereafter he made slow recovery; urinary specific gravity remained low and did not reach 1025 in the concentration test for three months, after which he was discharged from hospital. Weil–Felix, leptospiral agglutinins negative.

Case 2

A private aged 23 was admitted on October 24, 1951. History: back from Korea one week. Nausea, headache, abdominal discomfort, non-productive cough. T. 103.6° F., P. 100; clinical examination negative. Blood smears: no malaria parasites, blood culture sterile, W.B.C. 8,000 (P. 74%, L. 24%, M. 2%). Urine N.A.D.

3rd day.—T. 102° F. (38.9° C.) to normal. Felt dopy, but wanted to get up. Bowels loose, no vomiting. B.P. 105/85.

4th day.—Uncontrollable during the night but now afebrile. Petechiae in buccal and sublingual mucosa and in both axillae. B.P. 102/80, heart normal, chest *x*-ray film normal. Tender renal angles with backache. Urine: albumin 2 plus, granular and hyaline casts and red cells, sterile on culture. Diagnosed epidemic haemorrhagic fever.

5th day.—Severe backache, oliguria. B.P. rising, 120/90. Intermittent hiccup with abdominal distension. Epistaxis.

6th day.—Appeared bloated; hiccup severe, urine frankly blood-stained and more petechial haemorrhages in axillae and over limbs. B.P. 170/110. W.B.C. 34,000; differential count showed metamyelocytes 6% and myelocytes 3%; normoblasts early 0.5%, intermediate 5%, and late 3%. Blood urea 130 mg. per 100 ml.; Hb 77%; R.B.C. 4,300,000. Profuse epistaxis requiring morphine.

7th day.—Petechiae disappearing from mouth, extending over chest and abdomen and dorsum of feet; needle punctures ecchymotic. Hiccups less, brighter mentally. Recurrent epistaxes. Bleeding-time 3 minutes.

8th day.—W.B.C. 15,400; Hb 64%; blood urea 128 mg. per 100 ml. Urine less blood-stained.

10th day.—One pint (570 ml.) whole blood transfused. Blood urea 164 mg. per 100 ml.; W.B.C. 7,000; Hb 68%. No backache or abdominal pain. Felt well; B.P. 170/90. Urine blood-stained.

12th day.—B.P. 160/100. Urine showed heavy cloud of albumin, 10–20 R.B.C. and 3–4 W.B.C. per field; no casts seen. Diuresis began.

17th day.—Haematuria persisting, this continued until the 19th day.

21st day.—Blood urea, 37 mg. per 100 ml. Nocturia and diurnal frequency disappearing.

28th day.—B.P. 160/100. Developed a carbuncle on the neck, which cleared up with local treatment. He was evacuated to Australia five days later, feeling fit but unable to concentrate his urine.

Case 8

A gunner aged 26 was admitted on November 24, 1951. Onset of disease on November 15 with headache and fever.

3rd day.—Reported sick with cough, anorexia, and backache; T. 104° F. (40° C.), signs of bronchopneumonia. Treated with penicillin.

6th day.—Vomiting and abdominal pain; T. 102.6° F. (39.2° C.). B.P. 90/60, W.B.C. 26,000, white-cell precursors present.

7th day.—Afebrile. Anuric for 36 hours. B.P. 110/78. Conjunctival haemorrhage, epigastric tenderness, albuminuria, and haematuria noted. Patient became irrational.

8th day.—Voided urine, vomiting ceased. Restraint necessary to prevent patient escaping.

9th day—Drowsy, but ate breakfast. Complained of blurred vision. B.P. 120/80. N.P.N., 51 mg. per 100 ml.; W.B.C., 27,000 (P. 64%, L. 32%, M. 5%, E. 2%).

10th day.—Admitted this hospital. Both eyes showed conjunctival haemorrhages, petechiae noted in mouth and over chest and abdomen scantily. Breath uraemic. Pupils small. Sores around lips; sore throat, and submandibular adenitis. B.P. 150/100. Abdomen slightly distended, spleen and liver impalpable. Hyperreflexia but no meningism present. Urine albumin 1 plus. Fluids forced.

11th day.—Less drowsy. B.P. 130/80. Voiding urine normally.

12th day.—Blood urea, 230 mg. per 100 ml.; blood chloride, 363 mg. per 100 ml. Prothombin time 12 seconds (control 12.5 seconds). Urine: albumin 1 plus, 20–30 R.B.C., 3–4 W.B.C. per field and occasional hyaline casts seen. Urine chloride 1 g. per litre. Additional salt given orally.

13th day.—Blood urea 88 mg. per 100 ml. Albuminuria diminishing.

15th day.—Albuminuria ceased.

16th day.—Diuresis with nocturia, voiding four times during day and six times during night.

21st day.—Backache persisted, with some headache. B.P. 128/90. Nocturia now twice each night.

23rd day.—Blood urea 37 mg. per 100 ml.

28th day.—Evacuated home; unable to concentrate urine, but ambulant.

Case 9

A gunner was admitted on November 20, 1951, the sixth day of disease. While stationed near the River Imjin had onset of chills and frontal headache on November 12. Reported sick next day, as chills recurred in evening.

3rd day.—Passed no urine.

4th day.—Drenching sweats, backache, and delirium.

5th day.—T. 102° F. (38.9° C.). W.B.C., 6,000. Cough began.

6th day.—T. 102° F. (38.9° C.), P. 100, R. 30, cyanotic. Rhonchi heard in all lobes. B.P. 90/70. Urine contained albumin, granular casts, and few R.B.C.s. W.B.C. 8,000.

7th day.—Vomited for first time. Petechiae on palate. B.P. 120/84. W.B.C., 8,150; T. 99° F. (37.2° C.).

8th day.—Frequent vomiting, epistaxis, suppression of urine. Afebrile.

9th day.—Remained afebrile. Urine boiled solid, contained 5 g. chloride per litre. Blood chloride 370 mg. per 100 ml. B.P. 150/120, P. 56. Petechiae noted in mouth and axillae. Appeared dehydrated; intravenous saline given.

10th day.—Stopped vomiting. Urine output increasing, blood-stained. Blood chloride, 495 mg. per 100 ml.; blood urea, 248 mg. per 100 ml.; W.B.C., 7,500.

11th day.—Diuresis began, urine still blood-stained.

12th day.—Vomiting small quantities of bile-stained fluid. B.P. 140/90. Typical epileptiform convulsions repeated six times; treated by venesection followed by 2.7% NaCl and 5% glucose—250 ml. intravenous drip containing sodium lactate and bicarbonate to combat acidosis. Serum chloride, 550 mg. per 100 ml.; blood urea, 197 mg. per 100 ml.

13th day.—Settled, but drowsy and complaining of blurred vision. B.P. 155/115. W.B.C. 6,500, metamyelocytes present.

14th day.—Rational. No further vomiting. B.P. 150/110.

15th day.—Blood chloride 390 mg. per 100 ml. Urine: albumin 1 plus, 10–15 R.B.C. and 2–3 W.B.C. per field; occasional hyaline casts.

25th day.—Nocturia and backache the only symptoms. Albuminuria much diminished. No casts in urine, which contained 1–2 R.B.C. and 4–5 W.B.C. per field.

Pathology

One of our patients died. The following account, with post-mortem report, is provided by Captain Knudsen.

Patient left Korea on November 8, 1951. History of close contact with field mice. Onset of symptoms November 18, with headache, fever, and anorexia. Vomiting began on November 21, with developing oliguria. November 23; W.B.C. 64,000, numerous juvenile forms; blood urea, 112 mg. per 100 ml. Treated symptomatically and by intravenous fluids. November 25: severe epistaxis. November 26: melaena; Hb. 44%. Further epistaxis, increasing mental confusion, signs of circulatory failure. Death occurred on November 27 following vomit of about 1 pint (570 ml.) of altered blood, which was partly inhaled.

External appearances: the body was that of a well-nourished young man. Scattered petechiae were present. A sternal puncture mark was present over the first segment of the sternum. The conjunctivae were normal.

Internal appearances.—Pleural: parietal and visceral pleurae showed petechiae. No fluid present. Pericardium: both visceral and parietal showed numerous petechiae; fluid normal volume but deeply blood-stained. Heart: scattered subendocardial haemorrhages and haemorrhage into the cusps of the aortic and mitral valves; the myocardium was normal and the chambers were of normal size. Lungs: both lungs showed gross haemorrhage into their substance, mainly affecting the lower lobes; a moderate degree of oedema was present. Trachea and bronchi: the trachea and main bronchi contained bloody fluid similar to that present in the stomach, but were otherwise normal. Oesophagus: normal. Aorta: early atheroma and an area of subintimal haemorrhage 2 by 1 in. (5 by 2.5 cm.) in the arch. Thyroid: normal.

Abdomen: the peritoneum showed scattered petechiae; no free fluid; the stomach showed extensive submucous haemorrhages and contained several ounces of bloody fluid; the duodenum and small gut showed extensive petechial mucosal haemorrhages and contained bloody contents; the colon showed petechial haemorrhages but was less affected; pancreas normal; spleen normal size, with a few serosal petechiae and small haemorrhages into its substance. Suprarenals: both suprarenals were disorganized by gross haemorrhage; only a shell of gland tissue 1 mm. thick remained. Kidneys: normal size, capsule stripped easily, revealing numerous surface petechiae; on section there were scattered small haemorrhages into the cortex; the medulla was deep red (? haemorrhage ? congestion); the renal pattern was preserved and the vessels appeared normal; both ureters were normal; the renal pelves both showed small subepithelial haemorrhages. Liver: normal size, few surface petechiae. Gall-bladder: normal. Bladder and testes: normal.

Brain: skull and membranes normal; gross haemorrhage into the infundibular stalk and the pituitary gland; on section the haemorrhage was seen to involve the entire stalk and the periphery of the gland. The remainder of the brain was normal.

Cause of death: epidemic haemorrhagic fever with widespread haemorrhages and terminal inhalation of vomit.

Previous Reports

Death has usually occurred about the tenth day of illness. Haemorrhage into the kidney has been outstanding, haemorrhages into the suprarenal and pituitary glands are often found, and parenchymatous degeneration with diffuse capillary damage in many organs has been reported.

Discussion

The aetiology of this disease is not yet known. American workers in the field seem to be confident of a virus aetiology, but had been unable to corroborate the earlier Japanese findings at the time this report was written.

The disease resembles a non-icteric form of Weil's disease and may prove to be caused by a leptospire. Its prevalence along river banks and estuaries in North Korea during autumn months, the presence of a suitable rodent carrier in vast numbers, and its general clinical course, with special emphasis upon renal involvement, are all suggestive of such an infection despite the absence of positive proof by laboratory demonstration. Weil's disease has a case mortality of 3% for the age group 16–30 (Broom, 1951), our mortality was 1 in 40 (2.5%), but diagnosis was possibly made more often in milder cases owing to its epidemic quality. All agglutination tests for leptospirosis were negative. As renal failure in this disease follows a period of hypotension it may be due to anoxia, which Darmady and his colleagues (1944) suggest is the causative mechanism in Weil's disease; the pathological picture of the kidney is one of cortical pallor and medullary hyperaemia, suggesting an alteration in the distribution of blood flow in the kidney which may short-circuit the glomeruli, as has been shown in rabbits by Trueta *et al.* (1947). Paralysis of the sympathetic nerves by high spinal anaesthesia was not attempted in our cases.

The hypothalamic and pituitary lesions possibly have far-reaching effects upon the hormonal control of urinary secretion and upon the autonomic control of the vascular system, and may be responsible in part for the tendency to inversion of sleep rhythm noted in some of our cases. Adrenal cortical damage may be responsible for the prostration and electrolyte imbalance seen early in the disease and for the delayed water excretion and apparent lack of concentrating power of the kidneys in the later phases.

Summary

An epidemic disease broke out among our troops stationed in Korea during the autumn months of 1951; a summary of its characteristic features as seen in 40 cases treated at the British Commonwealth General Hospital, Kure, Japan, has been presented, together with some of its complications. Its aetiology remains obscure; its similarity to anicteric forms of Weil's disease is noted. Chemotherapeutic and antibiotic agents have been proved of doubtful value in treatment.

My thanks are due to Lieutenant-Colonel K. P. Brown, R.A.M.C., officer in charge of medical division, for reading this paper and making helpful suggestions. Grateful acknowledgments are due to all those medical officers who have assisted with their case notes of the patients they have treated. For permission to publish this paper I am indebted to Colonel J. E. Snow and the Director-General, Army Medical Service.

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The first standard nomenclature in malariology (*Report on Terminology in Malaria*) was published by the Malaria Commission of the League of Nations in 1940. It has now been revised by a drafting committee (Professor N. H. Swellengrebel, Sir Gordon Covell, and Dr. P. F. Russell) appointed by the World Health Organization, and is issued as No. 13 in the W.H.O. Monograph series. Part 1 of *Malaria Terminology* is a commentary on the terms used by malariologists and falls into three sections, covering the parasites and the infections to which they give rise, the measurement of malaria in the community, and the vector itself. Part 2 is a comprehensive glossary. The price of this publication is 5s.

PARALYSIS FOLLOWING POISONING BY A NEW ORGANIC PHOSPHORUS INSECTICIDE (MIPAFOX)

REPORT ON TWO CASES

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The purpose of this paper is to report two cases of paralysis which developed in the third week after the onset of symptoms of acute organic phosphorus poisoning due to a new compound, *bis*-(mono-*iso*propylamino)-fluorophosphine oxide. The common name recommended for this substance by the British Standards Institution is mipafox. Like other organic phosphorus compounds used as insecticides, mipafox is an inhibitor of cholinesterase *in vitro* and *in vivo*. Preliminary tests had indicated that the new compound was effective as an insecticide, and that the oral toxicity to rabbits and guinea-pigs was only a twenty-sixth of that of "parathion" (*Nature*, 1951).

In August, 1951, three people employed in the manufacture of a small quantity of this substance by a pilot process developed the symptoms and signs characteristic of acute organic phosphorus poisoning, and two were admitted to hospital.

Case 1

The patient, a female research chemist aged 28, had been employed on the development of organic phosphorus compounds for 21 months before admission to hospital on August 15, 1951. During this time she had handled a number of substances in this group, and, although her exposure to them was mainly in the laboratory, she was concerned occasionally in the manufacture of small amounts of new compounds in pilot plants. She had experienced symptoms of mild organic phosphorus poisoning on at least three occasions during this time, and was away from contact with organic phosphorus compounds for two or three weeks in June, 1951, following one of these attacks.

At about 8 p.m. on August 15, when she had been working long hours on the pilot-scale production of mipafox for three days, she began to feel sick and tired. She attributed these symptoms to fatigue, and continued at work although the symptoms became gradually worse. She left the factory at 12 midnight and returned to lodgings, where she was quite alone. At about 2 a.m. on August 16 she began to suffer from vomiting and involuntary defaecation, and this continued at intervals of a few minutes until 3.30 p.m., when she was given 1/50 gr. (1.3 mg.) atropine by intramuscular injection and admitted to Addenbrooke's Hospital under the care of Dr. A. P. Dick. The vomiting and involuntary defaecation were accompanied by cramps in the muscles of the legs, and by 5 a.m. generalized muscular weakness was so great that she was unable to get out of bed to seek assistance.

The administration of atropine relieved the vomiting and diarrhoea within half an hour, but nausea and muscular twitchings persisted. On admission to hospital significant findings were suffusion of the conjunctivae, pin-point pupils, twitching of the facial and sterno-mastoid muscles, and

diminished tendon reflexes. On August 17 hypotonia of all muscles was still a striking feature. The gastro-intestinal symptoms were controlled by atropine, administered at frequent intervals, but this did not affect the muscular twitchings. The total amount of atropine administered was 0.9 gr. (58.5 mg.) given in the following doses: August 16: 1/50 gr. (1.3 mg.) × 7; August 17: 1/50 gr. (1.3 mg.) × 9; 1/100 gr. (0.65 mg.) × 4; August 18: 1/75 gr. (1 mg.) × 1; 1/30 gr. (2 mg.) × 1; 1/50 gr. (1.3 mg.) × 20; August 19: 1/50 gr. (1.3 mg.) × 4.

On August 19 the patient developed delusions and hallucinations which were attributed to overdosage with atropine. When the atropine was discontinued her mental state returned rapidly to normal. She was symptom-free after four days and was discharged from hospital on August 31, the sixteenth day after her illness began. For several days she had been out of bed and had walked about the ward, apparently well.

As she walked downstairs to leave hospital she noticed for the first time weakness and unsteadiness of her legs. During the next three or four days there was little change in her condition, which then began to deteriorate. The weakness in the legs increased, and she noticed weakness of the hands and arms. These symptoms became gradually worse, and she was readmitted to hospital on September 10. On examination she was found to have a flaccid paralysis of both legs and weakness of the muscles of the thighs. The knee-jerks were diminished and the ankle-jerks absent. There was no plantar response. Although the legs and feet were cold and the muscles tender to palpation, there was no change in cutaneous sensation to pin-prick or light touch. Weakness of the muscles of the right hand was present.

The paralysis progressed, and the patient was transferred to the London Hospital on September 15 under the care of Dr. Donald Hunter. At this time there was complete flaccid paralysis of the lower limbs. The knee-jerks and ankle-jerks were absent and the plantar reflexes could not be elicited. Tone and power in the arms, forearms, and hands were greatly reduced. The biceps-jerk was just present, but neither the supinator nor the triceps jerk could be elicited. The trunk muscles were also weaker than normal. Cranial nerves were normal, there were no signs of involvement of the central nervous system, and no disturbance of cutaneous sensation could be demonstrated. All muscles, particularly those of the calf, were tender to palpation, and muscle twitchings were observed in the deltoids, facial muscles, and muscles of the legs.

Power returned gradually over a period of weeks to the muscles of the thighs, arms, and forearms. On October 20 power and tone were normal in the arm muscles and the tendon reflexes were present and brisk. There was weakness of the long extensors of the fingers, and the lumbricals and interossei were wasted and completely paralysed. In the lower limbs power and tone had returned to some extent in the thigh muscles and flexors of the hip, but the muscles of the leg below the knee were still flaccid and completely paralysed. There was marked wasting of the small muscles of the feet. Although there was no spasticity, the knee jerks were exaggerated and patella clonus could be elicited without difficulty. The ankle-jerks were absent. Fasciculation was still present in the deltoids, facial muscles, and muscles of the legs, and the patient complained of cramp-like pains, affecting particularly the muscles of the lower limbs. Alternating vasodilatation and vasoconstriction resulted in subjective symptoms of burning and coldness in the hands and feet, and these were accompanied by flushing or pallor and cyanosis.

In the first week in November the clinical picture was complicated by subjective evidence of sensory changes of glove and stocking distribution. On repeated examination the distribution of these changes was not constant, and at times the pattern was bizarre. It is possible that these symptoms were functional in origin, and they disappeared completely within a few weeks.

Between November, 1951, and February, 1952, slow improvement continued in the groups of muscles which had already begun to regain their normal function, but the muscles of the legs and feet remained completely paralysed. The wasting of the small muscles of the hands became increasingly obvious (Fig. 1), and it seemed likely at this time that no recovery could be expected in these muscles or in the muscles of the legs and feet. From the first week in April, 1952, however, the small muscles

FIG. 1.—Wasting of small muscles of hands; Case 1, six months after mipafox poisoning.

FIG. 2.—Case 1, recovery in hands five months later.

of the hands began to recover. Power returned slowly to the lumbricals, interossei, and opponens pollicis, and by July the wasting was much less (Fig. 2). In May the ankle-jerks were first elicited, and these were followed within a few days by the return of slight movement of the toes.

At the time of writing the upper limbs are normal. Power in the muscles of the thighs is almost normal, but is greater in the flexors than in the extensors. Although patella clonus can still be elicited it is much more difficult to demonstrate. Exaggerated ankle-jerks and ankle clonus are readily elicited and the plantar response is extensor on both sides. Movements of the toes are gradually increasing, and inversion and eversion at the ankle-joints are present but weak. Plantar flexion is strong, but there is little evidence of the return of power of dorsiflexion. For six months the patient has been able to go out in a wheel-chair, and is now able to stand with support.

Throughout the illness the right side has been more severely affected than the left in both upper and lower limbs, and is recovering more slowly. There has been a striking absence of trophic changes in the skin over the paralysed muscles. The cranial nerves have been unaffected at all stages of the illness, and no tremor or ataxia has been present at any stage.

Investigations

On August 17 the cholinesterase activity was as follows : Red blood cells (true cholinesterase), 9 units ; normal 75–142. Plasma (pseudo-cholinesterase) 1 unit ; normal 51–128 (Warburg technique). The results of subsequent estimations are shown in Fig. 3 and the Table. On September 19 lumbar puncture gave normal results. On September 20 the pyruvate tolerance test showed : 0 minutes, 0.92 mg. pyruvic acid/100 ml. blood ; at 60 minutes, nil ; at 90 minutes, 1.32 mg. pyruvic acid/100 ml. blood. (These results are within the normal range.) On October 5 visual fields were normal for white and blue objects. An electrocardiogram taken on October 10 showed physiological tracing.

Electromyographic Studies.—On September 19 the electromyogram showed a reduced interference pattern, but the individual motor units were normal. There was no activity at rest. Muscle stimulation showed complete reaction of degeneration in the lower limbs and partial reaction of degeneration in the thenar eminence. Further examination on September 21 showed the electrical responses to be equivocal and not definitely sluggish. Some polyphasic motor-unit potentials were found in the forearm extensors, but no fibrillation potentials. This is against a lesion producing lower-motor-neurone degeneration. On December 7 there was no response to 1 millisecond nerve stimulation, but a response to 100 millisecond stimulation, weakening on repetitive contraction ; spontaneous muscle-fibre activity ; motor-unit potentials were of short duration and all polyphasic. These findings are comparable with those found on the administration of a depolarizing drug such as decamethonium iodide, and suggest a state of neuromuscular block due to depolarization of the end-plate increasing on muscle contraction. On May 21, 1952, no decrease of muscle contraction on repetitive stimulation was demonstrable. Muscle fibrillation potentials were present, with definite evidence of lower-motor-neurone lesion. The picture was that of peripheral neuritis. There was probably some fibrosis of muscle, particularly in the gastrocnemius. Prognosis was now that for a peripheral neuritis.

Case 2

A chemical process worker, aged 39, was engaged with the research chemist (Case 1) in the manufacture of mipafox for five days before he became ill on August 16, 1951. He first noticed wheezing and tightness in the chest. This was followed by a sensation of pricking of the eyes accompanied by redness of the conjunctivae, constriction of the pupils, and difficulty in raising the upper eyelids. He gave up work and was given atropine sulphate 1/50 gr. (1.3 mg.) by intramuscular injection and sent home to rest in bed. Although the symptoms were relieved by the atropine they had recurred by next morning, when the patient was found to have bronchospasm, marked weakness and hypotonia of the muscles of the limbs, and constricted pupils which failed to react to light and accommodation. There was excessive sweating, particularly affecting the forearms.

He was admitted to Addenbrooke's Hospital under the care of Dr. A. P. Dick on August 17, with the symptoms and signs of organic phosphorus poisoning already described. He had experienced similar symptoms six months previously while working with a different organic phosphorus compound. On this occasion the symptoms subsided after he had been away from contact with the substance for two or three days.

Treatment with atropine sulphate 1/50 gr. (1.3 mg.) by intramuscular injection controlled the muscarinic symptoms as in Case 1, but attempts to reduce the dose resulted in a relapse on August 20. The doses of atropine given between August 17 and August 22 were as follows : August 17, 1/50 gr. × 5 ; August 18, 1/50 gr. × 22 ; August 19, 1/50 gr. × 11 ; August 20, 1/50 gr. × 7 ; August 21, 1/50 gr. × 17 ; August 22, 1/50 gr. × 8 ; making a total dose of 1.4 gr. (91 mg.). Mental disturbance suggestive of atropine poisoning occurred on two occasions, and disappeared when atropine was withheld. He was discharged from hospital, apparently well, on August 28.

Nine days later the patient became aware of weakness of the legs, associated with cramp-like pain in the muscles of the calves and feet. He first noticed these symptoms after riding a bicycle. The weakness of his legs progressed, and he was readmitted to hospital on September 11. There was weakness and loss of tone in the muscles of both lower limbs, particularly below the knee. The patient was unable to dorsiflex either foot ; the power of plantar flexion was absent in the right foot and weak in the left. The ankle-jerks were diminished and the plantar reflexes could not be elicited. Although the symptoms and signs of paralysis improved rapidly, he was transferred with Case 1 to the London Hospital on September 15 under the care of Dr. Donald Hunter. At this time there was lack of tone in the muscles of both lower limbs, and the upper limbs were also slightly affected. Power and movement in the left leg was diminished. On the right side dorsiflexion of the foot was very much impaired, and the power of plantar flexion was also diminished. Tendon reflexes were normal on the left side ; the ankle-jerk was diminished on the right. The plantar responses were flexor. The cranial nerves were normal. The affected muscles were tender to palpation, but no cutaneous sensory changes were present.

The patient's condition improved gradually, and he was discharged home on October 5 with bilateral foot-drop, more pronounced on the right side than on the left. There was wasting of the small muscles of the feet, particularly on the right side. Since his discharge from hospital there has been further improvement, but after six months he complained that he still became tired easily and could walk only two or three hundred yards before his feet, especially the right, became "floppy." There was at this time demonstrable weakness of both dorsiflexion and plantar flexion of the right foot, and, although the ankle-jerk on the right side could be elicited, it was less brisk than on the left.

At the time of writing the patient could walk two miles before he noticed any difficulty. Standing at his work, which he resumed ten months after the onset of the acute illness, causes low back pain, and it is at present necessary for him to have a sedentary job. He complains also of a dull aching pain in the right foot with exacerbations of cramp-like pain affecting the foot and calf muscles on the right. These occur most frequently at night, and are severe enough to wake him from sleep.

Investigations

On August 17 the cholinesterase activity recorded was : red blood cells (true cholinesterase), 15 units ; plasma (pseudo-cholinesterase), 10 units. The results of subsequent estimations are shown in Fig. 3 and the Table. On September 20 the pyruvate tolerance test read : at 0 minutes, 9.92 mg. pyruvic acid/100 ml. blood ; at 60 minutes, 1.28 mg. pyruvic acid/100 ml. blood ; at 90 minutes, 0.86 mg. pyruvic acid/100 ml. blood. (These results are within the normal range.) Lumbar puncture on September 21 showed nothing abnormal.

Electromyographic Studies.—On September 21 electrical stimulation showed a brisk response. Intensity duration curves were normal. An electromyogram showed a reduced interference pattern with normal motor-unit potentials and no spontaneous fibrillation potentials, suggesting that there was no lower-motor-neurone degeneration.

A Further Case.—Another man, working with Cases 1 and 2, developed acute symptoms, which were less severe than in those cases. Recovery was uneventful and no delayed effects developed. The results of cholinesterase estimations in this case are shown also in Fig. 3 and the Table.

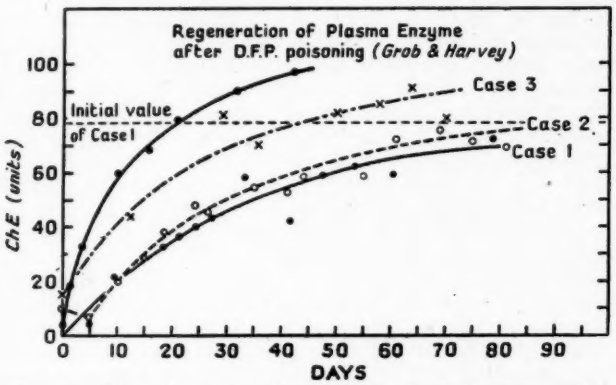

FIG. 3.—Rate of regeneration of plasma cholinesterase after mipafox poisoning compared with rate of regeneration following poisoning by D.F.P. (After Callaway, Davies, and Risley, 1952.)

Cholinesterase Activity (Warburg Units)

Days after Poisoning:		0	5	10	20	28	56	70
Case 1	R.B.C. ..	9	8	12	18	21	82	76
	Plasma ..	1	6	23	33	42	63	70
,, 2	R.B.C. ..	15	25	34	41	42	76	76
	Plasma ..	10	8	21	34	48	58	75
,, 3	R.B.C. ..	—	—	—	—	—	—	—
	Plasma ..	15	—	42	—	70	85	—

Treatment

Atropine, which is a specific antidote to the muscarinic and central-nervous-system effects of cholinesterase inhibition, was administered during the acute stages of poisoning. No antidote to the nicotinic effects is known and no treatment to counteract these was given either during the acute phase or after the onset of paralysis. Treatment of the paralysis included physiotherapy, which was limited because of the unusual fatigability of all muscles. This was particularly evident in the first patient. Ten weeks after the onset of paralysis, generalized muscular twitchings, clonic spasms affecting particularly the lower limbs, and a deterioration in her general condition were precipitated by an attempt to follow the routine of physiotherapy which would be usual for a patient affected to a similar degree by peripheral neuritis or anterior poliomyelitis. Occupational therapy was abandoned and physiotherapy was limited to passive movements, and from this time the patient made slow progress towards recovery, although the muscular twitchings recurred at intervals for four weeks. The administration of curare in small doses or of pseudocholinesterase preparations was considered, but, since the nature of the paralysis was so little understood, it was not thought justifiable to try either of these suggested methods of treatment.

Methods for the protection of persons handling organic phosphorus compounds in the manufacture, or in fields, orchards, or greenhouses, have already been described (Bidstrup, 1950). The need for regular estimations of blood cholinesterase activity in workers at risk was emphasized, and these cases illustrate the importance of making this test compulsory. Symptoms of poisoning may not develop until the cholinesterase activity is reduced to about 20% of normal, and removal from further exposure before this stage is reached may prevent serious illness and may save life.

Discussion

The use of organic phosphorus compounds such as hexaethyl tetraphosphate (H.E.T.P.), tetraethyl pyrophosphate (T.E.P.P.), and diethyl-*para*-nitrophenyl thiophosphate (parathion) as insecticides has resulted in many cases of acute poisoning (Grob, Garlick, and Harvey, 1950; Report to Committee on Pesticides, 1950). These substances, like the related compound di-*iso*propyl-fluorophosphonate (D.F.P.), inhibit the enzyme cholinesterase, and the symptoms and signs of poisoning have been attributed to the effects of inhibition of this enzyme. Although Abrams, Hamblin, and Marchand (1950) reported 30 fatal cases of poisoning among people engaged in the manufacture or use of these substances, no sequelae to acute poisoning were recorded among many patients who survived, and no chronic toxic effects were demonstrated in rats following prolonged administration of sublethal doses of these compounds (Barnes and Denz, 1951). Koelle and Gilman (1946) and Hunt and Riker (1947) had demonstrated persistent paralysis affecting particularly the hind limbs in dogs and cats following repeated sublethal doses of D.F.P., and A. Gilman (personal communication, 1950) suggested that the new organic phosphorus insecticides might be capable of causing in man a paralysis similar to the "ginger" paralysis described by Smith and Elvove in 1931.

"Ginger" paralysis was first observed in the days of prohibition in the United States of America in people who had been drinking Jamaica ginger contaminated with tri-*ortho*-cresyl phosphate (T.O.C.P.). Many such cases have since been described following accidental ingestion of T.O.C.P. (Sampson, 1942; Staehelin, 1941) or after exposure to T.O.C.P. during the manufacture of plasticizers (Hunter, Perry, and Evans, 1944). Hottinger and Bloch (1943) demonstrated that T.O.C.P. was an inhibitor of cholinesterase, and it was on this evidence that Gilman based his opinion that paralysis might follow repeated exposure to small amounts of the organic phosphorus insecticides. No such cases were reported until 1951, when Petry described paralysis in a man who had been using parathion in greenhouses in Germany and who had experienced symptoms of mild poisoning on several occasions. The onset of paralysis occurred almost three months after the last recorded exposure to parathion, but was preceded by severe "gastritis," and resembled closely in mode of onset and subsequent course the paralysis which follows poisoning by T.O.C.P.

R. H. S. Thompson (personal communication, 1951) has demonstrated that mipafox is an inhibitor of cholinesterase and has a selective action *in vitro* upon pseudocholinesterase occurring in white matter from the cerebral cortex. Barnes and Denz (1953) have produced paralysis in hens with mipafox, and also with D.F.P. and T.O.C.P., and have demonstrated demyelination in the peripheral nerves and spinal cord of the affected birds. Although Barnes and Denz were unable to produce permanent paralysis in rats and rabbits with mipafox, general weakness was observed and demyelination was found in the peripheral nerves and in the fasciculus gracilis in the cord. Tri-*ortho*-cresyl phosphate has a similar action to mipafox both on cholinesterase activity and in the ability to cause demyelination (Earl and Thompson, 1952a). The paralysis which developed in our patients is similar to that which follows poisoning by T.O.C.P.

There is nothing unusual in the manifestations of the acute stage of poisoning by an organic phosphorus compound in these two cases. Symptoms resulting from excessive stimulation of autonomic motor cells, from stimulation followed by paralysis of striate muscle, and from stimulation followed by depression in the central nervous system are characteristic of poisoning by substances which cause inhibition of the enzyme cholinesterase. The effects of different inhibitors vary at different sites of action, and in these patients there was little evidence of disturbance in the central nervous system. Mental changes occurred in both patients during the course of treatment with atropine. These may have been due to belladonna poisoning, but similar mental symptoms have been described in persons recovering from poisoning by other cholinesterase inhibitors.

The occurrence of paralysis in these two patients after a latent interval of approximately two weeks suggests a possible risk associated with repeated exposure to substances which irreversibly inhibit cholinesterase. In both these patients there is a history of previous mild poisoning by organic phosphorus compounds, and in the first patient,

who is more severely affected, three previous episodes are recorded. The third patient suffered relatively mild symptoms of acute poisoning, from which he recovered rapidly and completely. There is no evidence that he had previously experienced poisoning by organic phosphorus compounds. Koelle and Gilman (1946) were able to produce paralysis of the hind limbs in dogs following the administration of repeated sublethal doses of D.F.P., although recovery from a single dose appeared to be complete.

Recovery of normal cholinesterase activity after exposure to substances which inhibit the enzyme irreversibly depends upon regeneration of cholinesterase. After absorption of D.F.P. or T.E.P.P. the red-cell enzyme returns in linear fashion at approximately 1% per day, the plasma enzyme exponentially reaching normal after 40 days (Harvey, Lilienthal, Grob, and Jones, 1947). The rate of recovery of cholinesterase activity in our patients was studied by Callaway, Davies, and Risley (1952). They found that, although the rate of return of the red-cell-enzyme activity was similar to that following poisoning with T.E.P.P. or D.F.P., the plasma-enzyme activity returned more slowly. After D.F.P. poisoning the plasma enzyme had reached 60% of normal in ten days, whereas in these cases the recovery in this time was only 25%. After 40 days only 60% of the plasma-enzyme activity had returned in the mipafox cases, whereas, after D.F.P., recovery is complete in this time. Until normal activity is restored there is an unusual susceptibility to the effects of absorption of any anticholinesterase agent. The fact that both the patients who became paralysed were frequently working with such agents and had been affected by them in the months preceding the final acute episode may have contributed to the occurrence of the delayed effects.

The work of Earl and Thompson (1952b) suggests that lowering of the pseudo-cholinesterase may result in demyelination. They showed that the delayed paralysis in hens poisoned by T.O.C.P. is preceded by a marked lowering of the pseudo-cholinesterase activity of plasma, brain, and spinal cord which is present from the first to at least the tenth day after administration of T.O.C.P., and suggest that inhibition of pseudo-cholinesterase may be responsible for the demyelination which is the characteristic lesion in T.O.C.P. poisoning. Barnes and Denz (1953) conclude that the ability of mipafox, D.F.P., and T.O.C.P. to produce demyelination is not solely or directly related to the activity of these compounds as inhibitors of cholinesterase. Whatever may prove to be the explanation of these experimental findings, demyelination is the most likely cause of the symptoms and signs which persist in our patients, and these may be the result of the prolonged reduction of pseudo-cholinesterase activity which occurred in the early months of their illness.

In a review of the literature on anticholinesterase drugs Koelle and Gilman (1949) comment upon the similarity of the effects on muscular function produced by D.F.P. and T.E.P.P. (Harvey, Lilienthal, Grob, Jones, and Talbot, 1947) and the syndrome "ginger paralysis" which follows poisoning by T.O.C.P. They suggested that the "ginger paralysis" might be the result of the effects of the prolonged loss of cholinesterase at the neuromuscular junction. Three months after the onset of paralysis the clinical picture and electromyographic findings in Case 1 were comparable with those following the administration of decamethonium iodide, and suggested a state of neuromuscular block due to depolarization at the motor end-plate increasing on muscle contraction (A. T. Richardson, personal communication, 1951). Eight months after the onset of paralysis the changes in the electromyogram were those of a peripheral neuritis, and there was no evidence at this time of neuromuscular block. In our opinion prolonged failure of transmission of the impulse at the motor end-plate contributed to the paralysis in these cases in the early stages, and the onset of symptoms after moderate exertion in each case, at a time when the cholinesterase activity of the red blood cells and plasma was greatly reduced, lends support to this hypothesis.

Two of us (P. L. B. and J. A. B.) have more recently observed two men in whom hypotonia of voluntary muscles with diminished tendon reflexes persisted for at least two weeks after acute parathion poisoning, and in our opinion this clinical sign should be specially sought during convalescence from acute poisoning by organic phosphorus compounds. We are seeking confirmation of an impression gained from seeing a small number of people exposed to organic phosphorus compounds that hypotonia may be present without other symptoms or signs in persons in whom cholinesterase activity is below normal. This impression and our experience with the cases recorded in this paper suggest to us that patients who have had acute organic phosphorus poisoning should be kept at rest for a longer period after the acute symptoms have subsided, and that physical activity should be limited until a normal cholinesterase level is again established.

Summary and Conclusions

Two cases of paralysis beginning in the third week after poisoning by a new organic phosphorus compound *bis*-(mono-*iso*propylamino)-fluorophosphine oxide (mipafox) are described.

The clinical syndrome resembles closely that of poisoning by tri-*ortho*-cresyl phosphate ("ginger paralysis") and of paralysis in a German worker following the use of parathion, another organic phosphorus compound.

The cases are discussed in the light of recent work on inhibition of pseudo-cholinesterase, and of demyelination produced in hens by certain anticholinesterase agents.

Since it is now confirmed that certain organic phosphorus compounds which have the property of inhibiting cholinesterase may cause paralysis in man, substances in this group should not be recommended for use as insecticides or for other purposes until both acute and chronic toxicity has been studied in several species of animals.

The blood cholinesterase activity of workers at risk of absorbing organic phosphorus compounds should be estimated before and at frequent intervals during exposure to these compounds. No person in whom the blood cholinesterase activity is found to be reduced should be subjected to the risk of absorbing even small additional amounts of any cholinesterase inhibitor.

We are indebted to Drs. A. P. Dick and Donald Hunter for permission to publish these case records, and for advice and criticism in the preparation of the report. Mr. D. R. Davies, of the Chemical Defence Experimental Establishment, Ministry of Supply, has carried out the estimations of cholinesterase activity, Professor R. H. S. Thompson the pyruvate tolerance tests, and Drs. St. J. Buckler and A. T. Richardson the electromyographic studies. We acknowledge the help of many colleagues who have seen and discussed these cases with us, and particularly that of Dr. A. T. Richardson.

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PROGESTERONE IMPLANTATION IN HABITUAL ABORTION

BY

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The woman who suffers a series of spontaneous abortions has attracted clinical as well as theoretical interest for many years. The most striking feature of reports in the recent literature (Bacharach, 1940; Smith, 1948; Bevis, 1951; Bishop and Richards, 1952) is the uniformity of the results claimed for various methods of treatment; as these nearly all indicate a success rate of the order of 80%, it is perhaps surprising that any problem should still be thought to exist. Few clinicians, however, would regard the matter as settled, and the search for the best form of treatment continues. It seems that, in spite of eagerness to publish series of cases treated in various ways, there has been great reluctance to compare the results of treatment with what really happens in the absence of specific therapy, as opposed to what, on theoretical grounds, has been expected to happen, based, for example, on the calculations by Malpas (1938) and Eastman (1947). Since it is unlikely that all the forms of treatment, which according to their respective authors prove so successful, can be influencing the exciting causes of repeated abortion, real doubt arises whether these series of treated cases may not in fact be comparable with the populations described by Malpas and by Eastman—that, in fact, the prognosis for the untreated patient may be much better than has generally been supposed. An alternative explanation could be that psychic factors are of paramount importance and that all the treatments are effective simply by giving the needed psychological boost.

The key role of progesterone in the maintenance of pregnancy has long been appreciated both experimentally and clinically. The fact that the site of its production changes from the corpus luteum to the placenta at about the twelfth to sixteenth week of gestation has suggested that at this critical time, at which so many spontaneous abortions seem to occur, the smooth takeover may not be accomplished, leading to a temporary or permanent fall in progesterone production, which might be responsible for the abortions. There is also the possibility that, in the habitual aborter, production of progesterone may be inadequate at all times. For both these theoretical reasons, the administration of progesterone has been advocated, both in the treatment of threatened abortion and in the prophylaxis of habitual abortion. Since the intramuscular injection of progesterone is certain to lead to considerable fluctuations of the progesterone level within the body, such treatment, it would seem, might do more harm than good. The slow absorption of the steroid from fused pellets implanted beneath the deep fascia suggests that this mode of administration might well be more appropriate. Good results from this treatment have, in fact, been claimed (Bishop, Richards, and Doll, 1950; Bishop and Richards, 1952).

We have been interested in this problem for some years and have been implanting progesterone in the same way as Bishop and Richards since 1947, but, because we have remained unconvinced that the successes claimed in the past for any form of treatment have been justified, we have not hesitated to treat approximately alternate cases, leaving the remainder without specific therapy but receiving the usual antenatal care. (The control patients attending St. Helier Hospital were given inert oral tablets.) We thus have a series of untreated control habitual aborters, the outcome of whose pregnancies can be compared with that of the patients who were implanted.

We have also made use of this clinical material in the attempt, by studying pregnanediol excretion, to obtain evidence for or against the theories of progesterone deficiency outlined above.

Material and Methods

The patients in this series have attended University College Hospital or St. Helier Hospital. They have all had two or more consecutive spontaneous abortions before the twentieth week, and none has been included in whom complicating factors (such as positive Wassermann reaction, extensive cervical tear, uterine malformation, associated medical disease, etc.) of obvious potential significance had been found. Preliminary investigation had been extensive in some patients (such as those complaining of infertility and seen in the first place in the fertility clinic) or absent in the case of those referred from the antenatal clinic. The assignment to the control or the treated group was on the basis of alternate cases at St. Helier Hospital and at random at University College Hospital. Implantation, by the technique described by Bishop, Richards, and Doll (1950), of six 25-mg. pellets of progesterone within the gluteal muscles about 5 cm. below the iliac crest, was carried out as soon as the pregnancy was diagnosed, and, in any case, not later than the tenth week of gestation or the time of the earliest previous abortion.

The outcome of pregnancy is now known in 113 patients, of whom 53 were controls and 60 had received progesterone implants. The distribution of previous abortions and the numbers of primary and secondary cases (the latter having had full-term pregnancies before the abortion sequence) are shown in Table I.

TABLE I.—*Distribution of Previous Abortions and Division into Primary and Secondary Cases in the Patients Included in the Series*

	No. of Previous Consecutive Abortions				Primary	Secondary	Total
	2	3	4	More than 4			
Controls ..	33	15	3	2	42	11	53
Received progesterone implants	33	16	7	4	45	15	60
Total ..	66	31	10	6	87	26	113

Pregnanediol estimation was performed on first morning urine specimens by the method of Sommerville, Marrian, and Kellar (1948), or, prior to the publication of that method, by a modification of the Guterman procedure (Swyer, 1949a, 1949b). The drawbacks of first morning specimens, as compared with 24-hour collections, are fully appreciated, but the likelihood of obtaining repeated 24-hour collections from out-patients is, of course, small. In this series a total of 355 determinations of pregnanediol excretion were made, 203 being on specimens from the control patients or the treated patients before implantation, and 152 on specimens from patients after implantation. One or more assays were made on specimens from 43 treated and 43 control patients; in each group, 18 patients provided

five or more consecutive specimens on which assays were made. In addition, 47 patients taken at random from the antenatal clinic were asked to provide a first morning specimen, on which pregnanediol assay was performed.

The Outcome of Pregnancy

Of the 60 patients who received progesterone implants, 48 were delivered of live babies, 11 aborted before the twentieth week, and one, who had previously had four pregnancies, none of which went beyond the twentieth week, delivered at 27 weeks a live baby which survived only five hours. In terms of living children, therefore, there was a successful outcome in 80% of cases. There were three caesarean sections for obstetric indications and one breech delivery. One patient delivered at 36 weeks a premature baby which survived.

Of the 53 patients who received no specific therapy, 40 were delivered of live babies and 13 aborted. A successful outcome was thus obtained in 75% of cases. There were two caesarean sections and two twin pregnancies, all of which were successful. One patient delivered at 34 weeks a premature baby which survived.

For the entire series (Table II) the success rate was 77.9%, and it is clear that the difference in the outcome for treated and untreated patients is not statistically significant

TABLE II.—*Outcome of Pregnancy in 113 Patients with Two or More Consecutive Previous Abortions*

	Aborted	Live Birth	Total	% Success
Controls	13	40	53	75·5
Received progesterone implants	12	48	60	80·
Combined ..	25	88	113	77·9

($\chi^2=0.124$, $P>0.7$), since a far greater difference could easily occur merely on a chance basis.

It will doubtless be objected that patients with a history of only two previous consecutive abortions are not necessarily "habitual aborters" and that therefore our series might contain a considerable number of patients whose previous abortions were due to the operation of non-recurrent chance factors. For these, progesterone implantation would not be expected to affect the outcome of subsequent pregnancies, so that a difference between control and treated groups would not be anticipated. The likelihood of such a "dilution" is, in fact, shown by the comparatively small number of women who do have more than two consecutive abortions, there being only 47 cases with three or more abortions in our series, which is drawn from more than 12,000 pregnant women. The distribution of these patients (Table I) is 20 controls and 27 implanted cases; the outcome of their pregnancies is given in Table III, from which

TABLE III.—*Outcome of Pregnancy in 47 Patients with Three or More Consecutive Abortions*

	Aborted	Live Birth	Total	% Success
Controls	9	11	20	55·0
Received progesterone implants	7	20	27	74·
Combined ..	16	31	47	66·

it will be seen that in the treated group the success rate was 74%, while in the control group it was 55%, the combined success rate being 66%. The difference between control and treated groups is not statistically significant ($\chi^2=1.107$, $P>0.2$), the likelihood of such a difference occurring on a chance basis being greater than 1 in 5. However, reference to Table I shows that the record of the previous abortions of the patients in the treated group is, in fact, worse than that of the control patients (11 with four or more abortions in the former, as against only 5 with four or more abortions in the latter); although this difference is a random sampling effect, it does seem possible that, had the control group had an equally bad past obstetric history, the difference in outcome of pregnancy for the two groups might have been greater. All we can say, therefore, is that our limited data do not give clear evidence of a beneficial effect from progesterone implantation, and that the outcome of pregnancy in the untreated patients was far better than would have been expected on the basis of the calculations of Malpas and of Eastman.

Pregnanediol Excretion

In order to see whether different patterns of pregnanediol excretion are found in habitual aborters with and without progesterone implants, and in unselected antenatal

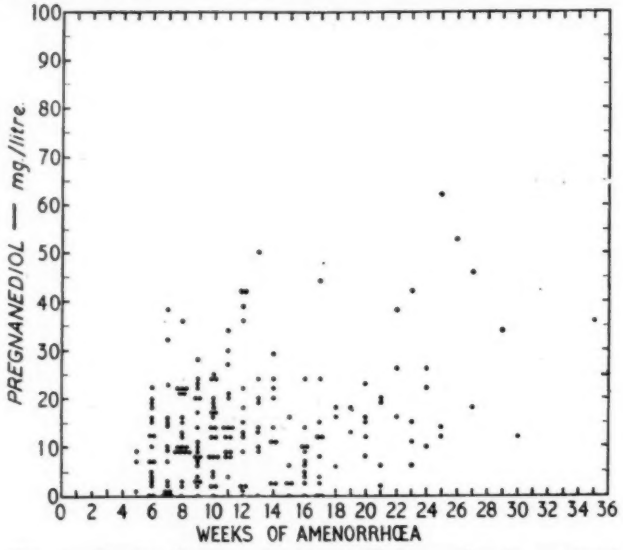

FIG. 1.—Scatter diagram of pregnanediol excretion in untreated habitual aborters.

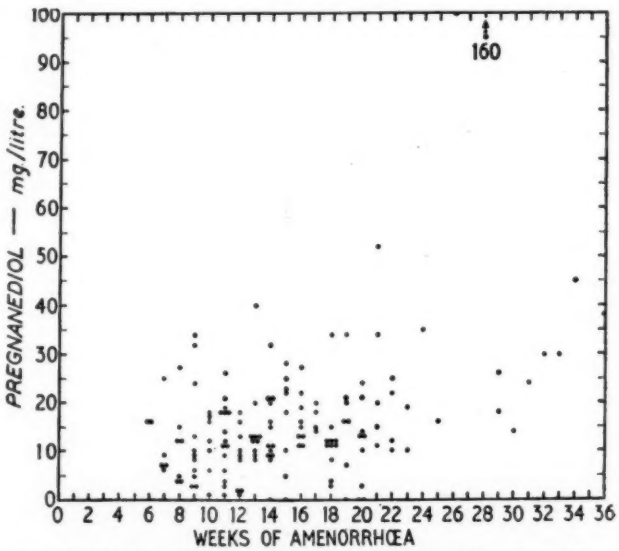

FIG. 2.—Scatter diagram of pregnanediol excretion in habitual aborters treated with progesterone implants.

patients, the assay values have been plotted in relation to the period of gestation to which they refer (Figs. 1 and 2). It is at once evident that wide scatter is seen in the first two groups and that no distinct differences are apparent.

Further analysis of the data was made by studying the regression of pregnanediol excretion on period of gestation for the three groups by standard statistical methods. Because relatively few assays were performed during the later stages of pregnancy, and because the variance seemed to increase during these stages, it was decided that it would be

safer to exclude all values obtained after the twenty-fifth week. Calculations were therefore based on 198 values in the control habitual aborter group, 141 values in the treated habitual aborter group, and 44 values in the unselected antenatal group. In the first place, it was found that in each group the slope was significant and that there was no significant departure from linearity (Table IV). It therefore became permissible to compare the three linear regressions (shown in Fig. 3). The analysis of variance for differences between the individual slopes and positions of the regression lines is given in Table V. It shows that there is no significance in the differences between the slopes (it will be recalled that to determine the unselected antenatal group regression line only roughly one-third the number of assays were used as were available for the other two lines, which are obviously indistinguishable). There is, however, a significant variation about the regression of the group means—that is, the relative positions of the lines. This indicates that the regression line for the unselected antenatal group is, if anything, placed at a lower level than that of the other two.

The data, therefore, do not provide evidence for a diminished output of pregnanediol in the habitual aborters, as compared with unselected antenatal patients, or for an increase in pregnanediol excretion in those habitual aborters who were given progesterone implants.

TABLE IV.—*Analysis of Variance for Slope and Departure from Linearity*

Group	Sources of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F.
Control habitual aborters	Linear regression	813·39	1	813·39	7·57†
	Departure from linearity	2,539·85	19	133·68	1·24
	Residual	19,010·1	177	107·402	—
	Total	22,363·34	197	—	—
Treated habitual aborters	Linear regression	574·40	1	574·40	7·11†
	Departure from linearity	1,740·51	18	96·70	1·20
	Residual	9,769·93	121	80·743	—
	Total	12,084·84	140	—	—
Unselected antenatal patients	Linear regression	412·83	1	412·83	6·09*
	Departure from linearity	1,058·44	13	81·42	1·20
	Residual	1,965·43	29	67·773	—
	Total	3,436·7	43	—	—

* Significant ($P<0.05$). † Highly significant ($P<0.01$).

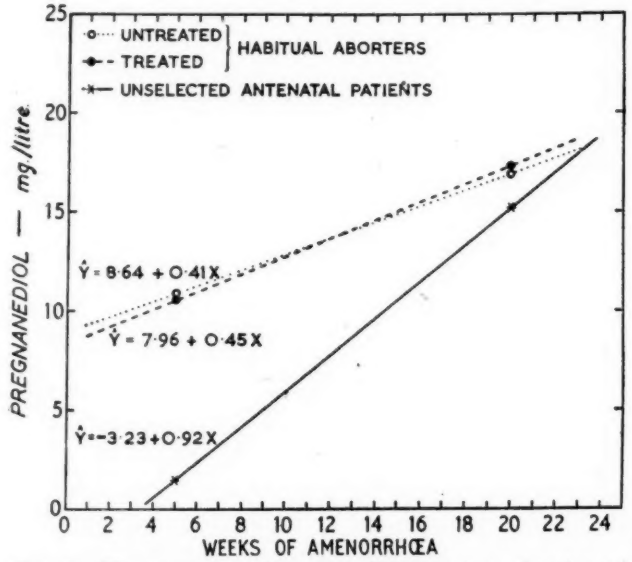

FIG. 3.—The regression of pregnanediol output on duration of pregnancy for treated and untreated habitual aborters and for unselected antenatal patients.

TABLE V.—*Analysis of Variance for Difference Between Slopes and Position of Regression Lines*

Sources of Variation	Sum of Squares	Degrees of Freedom	Mean Square	F.
Overall slope	1,455·47	1	1,455·47	15·47†
Difference between individual slopes	116·66	2	58·33	0·62
Difference between average slope and slope of group means	261·37	1	261·37	2·78
About regression of group means	399·94	1	399·94	4·25*
About individual lines	5,338·79	50	106·776	1·136
Residual	30,745·46	327	94·023	—

* Significant ($P<0.05$). † Highly significant ($P<0.01$).

Trends in Pregnanediol Excretion

In 18 control and 18 treated habitual aborters five or more consecutive pregnanediol assays had been performed. In studying these, it seemed that for each group three main patterns of excretion could be postulated, though, as will be seen in Figs. 4 and 5 which attempt to display the data, this conclusion might appear to be rather far-fetched. It seemed, however, that one group of patients produced a pattern of excretion which began at low levels and rose more or less steadily; a second group had an irregularly fluctuating pattern, with no marked tendency to climb during the first 25 weeks or so; while in a third the general tendency was to show relatively high levels in the early

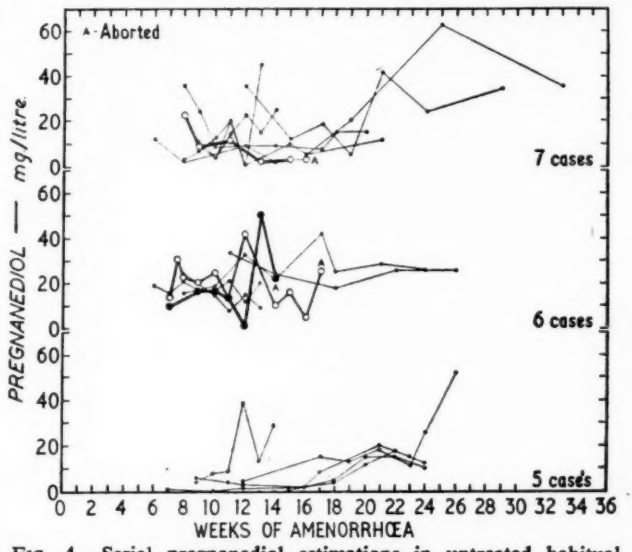

FIG. 4.—Serial pregnanediol estimations in untreated habitual aborters.

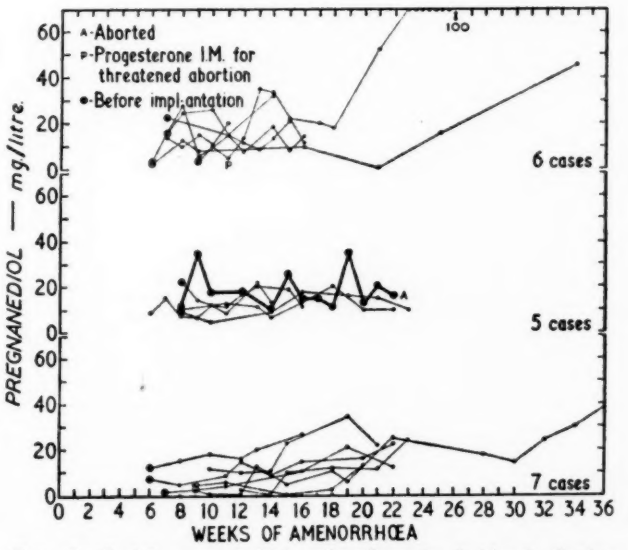

FIG. 5.—Serial pregnanediol estimations in habitual aborters treated with progesterone implants.

stages of pregnancy, but to fall later on. This last is the pattern referred to earlier as a theoretical possibility in habitual abortion; it occurred in seven out of the 18 controls and in six out of the similar number of implanted habitual aborters studied, and perhaps, therefore, strengthens the theoretical argument. It is doubtful, however, whether progesterone implantation has had the desired effect of eliminating the occurrence of the postulated fall in pregnanediol excretion. Perhaps the dose administered was grossly inadequate. If a fall in progesterone production, after an initial adequacy, is in fact an important cause of habitual abortion, it is not surprising that no overall deficiency of pregnanediol excretion in the habitual aborter group is apparent.

Further information on the causal connexion between failing progesterone production, as reflected by diminishing pregnanediol excretion, and abortion can be obtained by examining the pregnanediol assay values in those patients in the series who aborted. There were 15 patients who aborted and on whom pregnanediol excretion studies had been made; six of these were controls and nine had had implants. Of the controls, four showed low pregnanediol excretion, but in the other two adequate values were obtained, an output of 22 mg. being recorded on the day one of them aborted. Of the treated patients, only one showed an indubitably low value, the excretion being probably or certainly adequate in the remainder—for example, values of 12, 14, 15 mg. on the actual day of abortion. These data therefore suggest that a high proportion of the abortions in this series have occurred in spite of apparently adequate progesterone metabolism. On the other hand, one of the implanted patients, whose pregnanediol excretion fell and who threatened to abort, was given progesterone by intramuscular injection; the threat passed off, the pregnanediol excretion rose (Fig. 5), and eventually the pregnancy terminated successfully. Clearly, then, progesterone deficiency could be responsible for some of the tragedies.

Discussion

In their first series Bishop, Richards, and Doll reported on 45 cases of habitual abortion treated by progesterone implantation, the success rate being 86% for those patients who had had two previous abortions, 89% for those with three, and 75% for those with four or more. They compared these results with the calculations of Eastman on the expected outcome of pregnancy after repeated abortions, and concluded that, provided the true incidence of recurring abortions is not much less than 0.1%, their treatment had been of real value. In their second series Bishop and Richards added a further 40 cases, and for the combined group of 85 patients the success rates were 85%, 76%, and 67% for patients with histories of two, three, and four or more previous abortions respectively. Their conclusions remained unaltered, though they acknowledged the report by Bevis (1951) on 32 patients with three or more successive abortions, who had 81% of live births without any specific therapy but who had been subjected to extensive investigation.

The question naturally arose whether the similarity of the results was not, in fact, due to the psychotherapeutic effects, both of extensive investigation and of progesterone implantation. They wrote: "There is, of course, an obvious way of settling the question whether a progesterone implant is endocrinologically or merely psychologically therapeutic—namely, to treat alternate cases with implants of progesterone and an inert compound such as cholesterol." The present report, though not fulfilling these criteria, in that our control patients received no specific therapy, would seem to provide no strong support for the endocrine therapeutic efficacy of progesterone implants. However, the data from our control patients raises some doubt about the validity of the Eastman calculations.

A number of objections can be raised, both against these calculations and against the principle of comparing the results of treatment of a condition in one population with the outcome of that condition (whether untreated, treated in the same way, or treated in a different way) in another population and at another time. Since most of the latter are fairly obvious, we may confine our attention to the former. Eastman's calculations make the assumption that 10% of all pregnancies terminate in spontaneous abortion and that a recurrent factor causes 0.4% to abort repeatedly. Both these assumptions are dubious, the true incidence of spontaneous abortion being unknown but very likely higher than 10%, while the 0.4% is simply the incidence Bishop (1937) had found for women with two or more recurrent spontaneous abortions before the fifth month in a series of 2,687 cases at Guy's Hospital. In that same series the incidence of three or more spontaneous abortions was 0.1%—but this was constituted by no more than three cases. Another fallacy in the argument is the concept of a "recurring" factor. While it is true that such a factor may exist in every pregnancy in some woman (such, for example, as a gross uterine malformation), it is equally true that factors may recur in some of a series of pregnancies but become non-operative later. The effect of maternal syphilis is an obvious instance, while it is also well known that the changes undergone by the uterus during each pregnancy make it better adapted to accommodate a subsequent one. The frequent occurrence of abortion–premature stillbirth–livebirth sequences bears testimony to the waning influence of "recurrent" factors, at least in some patients.

Eastman's calculations lead to the prediction that the spontaneous cure rate would be 86.8% after one abortion, 63.1% after two abortions, and 16.4% after three. If his calculations are extended one stage further the predicted spontaneous cure rate after four abortions would be 2%—a figure with which few obstetricians of experience would agree.

Malpas's figures, based on similar calculations, were comparable—78% after one, 62% after two, 27% after three, and 6% after four abortions. The results we obtained in the control group—75% for 53 patients with two or more previous consecutive abortions, and 55% for 20 patients with three or more abortions—are clearly quite different from the predicted figures, and suggest either that the population we were sampling was not comparable with those which provided the basis for the Malpas and Eastman calculations or that those calculations were themselves fallacious. We incline towards the latter possibility.

Our data on pregnanediol excretion, though far from conclusive, give but little rational support for the use of progesterone implantation in the way we have employed it (which was the same as that used by Bishop and Richards). It is, of course, well known that pregnanediol is not the only metabolite of progesterone, and it is generally conceded that pregnanediol excretion may not reflect at all accurately the actual levels of progesterone turnover. Nevertheless, some difference would certainly have been expected between its excretion in habitual aborters and in "normal" patients, as well as between that of the controls and the implanted patients, if habitual aborters were deficient in progesterone and implantation corrected that deficiency. Moreover, though our data do provide some evidence for the occurrence of a temporary fall in progesterone production in some cases, implantation did not appear to lessen the incidence of such a fall. Finally, several of the abortions in our series occurred while pregnanediol excretion was apparently adequate, thus suggesting other causal factors.

The full discussion of these other factors is outside the scope of this paper, though mention should at least be made of germ-plasm defects, which, as Streeter (1931) has stressed, may be a more important cause of abortions than abnormal uterine environment, the factor favoured by Mall and Meyer (1921). Strong evidence in support of this theory comes from the studies of Hertig and Rock (1949), who recovered a series of 28 early human ova, 12 of which were abnormal in spite of perfectly normal endometria, and who

concluded, ". . . the evidence, such as it is, indicates that the defective fertilized ovum is due to intrinsic germ-plasm quality rather than to its environment, and is the main factor in the production of spontaneous abortion." If this view be correct, a therapeutically nihilistic attitude towards spontaneous abortion, be it isolated or repeated, seems inevitable until such time as we can exert a more direct influence on the germ-plasm itself.

We must, however, mention the report by Jones and Delfs (1951), who studied extensively the endocrine patterns in women with histories of abortions, and who based therapy (with thyroid, progesterone, and vitamin E) on the finding of deficiencies of these factors. There were 74 pregnancies in their series in women who had had three or more consecutive abortions; 41 gave indications of hormone deficiency and were treated appropriately, 35 going to term (85% success); 23, also apparently deficient, were left untreated, and only five went to term (22% success); while 10 patients who presented no evidence of hormone deficiency were given no treatment and had five term pregnancies (50%). It is difficult to reconcile these figures with our own, but it may be pointed out that the considerably greater success rate in the treated deficient cases, as compared with the untreated non-deficient cases, seems to argue strongly in favour of a psychological effect of the treatment, in addition to, if not in place of, its endocrinological effect.

Summary

The outcome of pregnancy in a series of 113 women who, prior to the pregnancy in question, had had two or more consecutive spontaneous abortions before the twentieth week has been studied. The 53 control patients, who received no specific therapy, produced 39 live babies (75% success); 60 patients received implants of six 25-mg. pellets of progesterone and gave birth to 48 live babies (80%). This difference is not significant. In the control group 20 patients had had three or more consecutive abortions and produced 11 live babies (55%); in the implanted group 27 patients had had three or more previous abortions and produced 20 live babies (74%). Again the difference is not significant. The success rate for the control group is far higher than currently accepted estimates would have had one expect, and the calculations on which these estimates have been based are criticized.

Studies of pregnanediol excretion on these patients provide no support for the view that progesterone deficiency is an important cause of repeated abortion, and failed to show any influence from the implanted progesterone. They gave some evidence for the development of a temporary fall in progesterone production in some cases, but none for the reduction of the incidence of such a development in the implanted patients. Many of the abortions seemed to occur in spite of adequate pregnanediol excretion.

If, as seems likely, germ-plasm defects account for more abortions than do abnormalities of uterine environment, a pessimistic view of any therapeutic attempts appears justifiable. On the other hand, the prognosis for the untreated patient who has suffered a series of abortions in former pregnancies may be much better than has hitherto been supposed.

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PAIN IN THE TRUNK

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Symptoms referable to the moving parts of the body are often encountered in both physical and psychological medicine, and considerable difficulties are apt to attend differential diagnosis. On the one hand, pain, though of organic provenance, may continue unaltered for long periods without giving rise to much in the way of physical signs. This is a particularly common feature of symptoms occurring in the trunk, and it is a well-known fact that backache, for example, may continue without appreciable alteration for years. On the other hand, pain of equal persistence setting up no objective signs to explain its source characterizes a number of psychogenic disorders. Moreover, nothing prevents a psychiatrically ill patient from developing a disorder of the moving parts irrespective of the mental state. Problems then arise that can be solved only by close collaboration between the two disciplines concerned.

It is our common experience that patients with purely psychiatric disorders have often received some years' physiotherapy before the true nature of their symptoms has been realized. Again, we find that, in a patient with obvious neurosis, symptoms of organic origin are often mistakenly dismissed as part of the psychiatric syndrome. Once detected, organic disorders can frequently be successfully treated in their own right, irrespective of concurrent psychiatric disability.

We have found that the greatest difficulties arise when the complaint is of pain in the trunk. Some cases are first seen in the psychological medicine, others in the physical medicine, department.

While we concern ourselves here with symptoms and signs affecting the back, exactly similar considerations apply to the other moving parts of the body. Our purpose in dealing with a restricted field is to draw attention to the fact that much so-called neurotic backache has an organic component. A relatively simple physical examination on the one hand and the consideration of various psychiatric criteria on the other make it fairly easy to decide how much weight to give to each factor.

Physical Examination

Since the disorder may show itself purely subjectively, the patient should be examined in a subjective way. In other words, many movements are tested, and each time the patient is asked whether or not the movement hurts. A pattern thus emerges that identifies the organic lesion, if there is one. If a muscle is strained, its contraction against resistance must hurt, but not the contraction of other muscles, nor such passive movements of joints as do not stretch that muscle. Alternatively, if complaint and signs indicate an articular lesion, muscle signs must correspondingly be absent. If one movement is limited at a joint, others are always limited too in a known proportion—and so on. All this is obvious enough to medical men but far from clear to patients, who, when an organic lesion is absent, will be found to answer at random, since they cannot tell whether some passive or resisted movement should hurt or not, be strong or weak, be limited or of full range; hence an incongruous pattern emerges. However neurotic a patient may be, if he has an organic lesion the pattern that he puts forward is on the whole tidy and self-consistent. If he has none, his emotionally determined answers contradict each other (if viewed as symptoms of a physical lesion) and quickly reveal the absence of a local disorder.

The physician should work out a routine for himself. He must start by examining a part of the body from which the alleged symptoms could not spring, passing on to relevant regions later. For example, if movement of the scapula or arm sets up as much lumbar pain as the lumbar movements themselves do when tested later, great doubt is thrown on the presence of an organic lesion.

The proper examination of any part of the spinal column involves:

1. Inspection of the whole trunk. Some postures are diagnostic in themselves—for example, spondylitis deformans—or a localized kyphos may be visible.

2. Noting the range and degree of painfulness of each *active* movement of neck, thorax, and lower back. For example, in thoracic spondylitis deformans it is the limitation of movement seen on lumbar spinal movements that explains the cause of the pain in the chest.

3. Testing the muscles about the joint while this is held still—that is, the *resisted* movements.

4. Testing the joint while the muscles are relaxed—that is, the *passive* movements.

5. Testing for dural pain—that is, pain in the trunk elicited by neck-flexion.

6. Testing the mobility of the nerve-root at the intervertebral foramen (lumbar spine only). The third lumbar nerve is tested by prone-lying knee-flexion, and the fourth and fifth lumbar and first sacral roots by straight-leg raising.

7. Testing conduction along the relevant nerve-roots. At the lower four cervical joints the pattern of muscle weakness identifies the level of a root palsy (Cyriax, 1950). The same applies to the third lumbar to the first sacral nerve roots.

8. Testing conduction along the spinal cord (cervico-thoracic spine only). Central disk protrusion, meningioma, and neuroma may compress the spinal cord and set up a spastic paralysis in the lower limbs, with resultant incoordination and extensor plantar response.

9. Palpation for deformity. An angular kyphos at the thoraco-lumbar spine characterizes hemivertebra, tuberculous caries, wedge-fracture, secondary malignant deposit, senile osteoporotic collapse of one body, adolescent osteochondritis, and complete erosion of two adjacent intervertebral disks. A shelf at the lower lumbar region shows the presence of spondylolisthesis. When this is of the concealed variety—that is, present on inspection, palpation, and radiography only when the patient stands—a diagnosis of psychogenic pain is commonplace.

10. Radiology.

11. Occasionally, contrast myelography. This is worth performing only in case of pressure on the spinal cord or suspected neuroma of the cauda equina.

Though this may seem a formidable list of diagnostic procedures, clinical examination does not in fact take long. As the examination continues, the confusion of the psychiatric patient's answers becomes increasingly obvious as his responses identify the "lesion" as existing about this joint, then near another; first at a muscle, then at a joint or nerve. Final correlation of his answers reveals a self-contradictory pattern inconsistent with any organic lesion. By contrast, whether neurotic or not, the answers of a patient with an organic disorder are not confused; for he describes a congruous pattern. The positive findings are consistent with each other, and all point to the same structure. On the negative side, when irrelevant movements are tested, these are all stated by him not to be painful, weak, or limited.

Some minutes' examination of the trunk—or indeed of any moving part—on these lines serves to single out from the patients attending a physical medicine department those who have purely psychological symptoms, and also to identify local lesions in those whose obvious emotional state has led to primary reference to the medical psychologist. The malingerer also declares himself clearly.

Back Pain as a Psychiatric Symptom

Pain in the back is not usually the presenting symptom in psychiatric illness. While it is our common experience that the vast majority of complaints of pain in the back have some organic foundation, there are some typical pictures of psychogenic back pain. Over-simplifying these typical syndromes for the sake of clear presentation, we may describe: (1) vague aches and pains all over the back (and often involving other parts of the body as well)—for example, Case 5. (2) Soreness, and/or throbbing and/or aching, at the site of an old usually well-remembered lesion, the physical effects of which have quite obviously passed off, the character of the pain lately having changed. (Often such a complaint relates to the site of a blow or injury—for example, Case 6.) (3) Pain likened to a knife or a red-hot poker, radiating up and down the spine, and extending characteristically into the occiput and other parts of the head. In some hysterical patients lumbar puncture is the precipitating factor. (4) Bizarre complaints of painful experience felt in the back, occurring in schizophrenic, paraphrenic, hypochondriacal, and organic mental conditions. While these complaints are part of a general psychotic picture, organic disease is occasionally also present. (5) The neurotic elaboration and overstressing of pain due to organic conditions such as arthritis, dysmenorrhoea, disk lesions, etc. The overt neurotic reaction may command so much attention that the organic factor becomes overlooked.

Differentiation of Physical and Psychogenic Pain

The differentiation of organic from psychogenic pain in the back follows standard lines. The criteria available are not completely satisfactory or foolproof. The recognition of well-known organic and psychiatric syndromes is assumed, and the case of the carefully briefed malingerer is disregarded. The main points are:

1. *Description of Pain.*—Too much reliance should not be placed on the manner of description, but organic pain is described with apt affect, having regard to the general make-up of the person. Psychogenic pain is described with affect that is often inapt or incongruous—the well-known overstressing of symptoms, or the less obvious indifference about an apparent disablement.

2. *Localization of Pain.*—Organic pain is generally localized, or spreads in one direction only. The patient is able to demonstrate unequivocally the site and radiation of his symptoms. Simple terms are used—slight, severe, bad, colicky, burning, etc. Psychogenic pain is often diffuse; radiation is often variable, in the patient's description and on questioning; location becomes vague on an attempt at delineation. The pain is often difficult to describe and the patient tends to indicate the extent of the suffering instead.

3. *Precipitating Factors.*—In organic disorder these are usually well known and identifiable by the patient, even though on occasion he may tend to withhold them as "too silly"—for example, turning the head to look sideways may initiate pain behind the shoulder-blade. Tact may be needed to elicit the known precipitating cause. In psychogenic pain these are usually vague—"comes on for no reason," or imputed to "overwork," "overstrain," but infrequently to "worry" as such.

4. *Relieving Factors.*—In organic pain these are recognized; but again, in some conditions, particularly slipped disk, may be withheld—for example, packing neck with two pillows—as "silly." In psychogenic pain these are often vague—or at times a little *outré*. They are, however, rarely withheld, as the patient exploits them on occasion; massage, special arrangements of lights, and even spontaneously discovered trance-states may be employed (Gould, 1953).

5. *Previous History.*—In organic pain the history generally reveals marked physical trauma, but this may at times be noticeably absent—for example, lumbago coming on after some hours' sitting. In the simple case no overt history of psychiatric stress is obtained. Particularly in relation to movement of a fragment of an intervertebral disk, the precipitating activity may be quite minor or banal. In psychogenic pain the extended psychiatric history reveals evidence of emotional stress to which the patient has responded by the production of neurotic symptoms at critical periods from school-going, puberty, etc., onwards. There may be a history of neurotic reaction—perhaps resembling in some respects the present symptoms—which resolved more or less completely with or without treatment, treatment (if any) having been psychiatric or apparently suggestive.

Psychogenic causation of current symptoms may be regarded as established when the onset of the symptoms can be traced to one or more sources of significant emotional stress. This does not necessarily exclude a coincidental physical cause. Sometimes one may be able to establish antecedent and apparently causally related psychogenic factors, and yet judge, from the behaviour of the individual in similar circumstances at other times, that these factors are relatively unimportant on this occasion.

In spite of the usefulness of these criteria, cases may be encountered in which one is able to build up a suggestive chain of events indicating psychogenesis, and yet find the total personality and the past history so out of keeping with the diagnosis of psychogenic pain that the latter is doubted and further physical examination is advised.

Identification of Organic Pain in a Psychiatrically Ill Person

Provided one is well acquainted with the pattern of the psychiatric illness and the symptoms to which it gives rise in the individual case, this may prove a relatively simple matter. Symptoms more or less closely corresponding to those mentioned above under the organic heading may make their appearance; yet the symptomatology of the established neurosis persists. Furthermore, the patient's attitude to the symptom is usually much more matter-of-fact. In addition, from a psychiatric point of view, no "purpose"—symbolic or "practical"—appears to be served by the symptoms. In such cases it is possible to treat the local lesion in its own right by appropriate methods, and to relieve the patient of the organic symptoms while leaving the neurotic pattern unchanged. In other cases, however, the physical symptoms become neurotically elaborated (see Cases 1, 2, and 3).

Psychiatric Illness Presenting with Local Spinal Symptoms

The technique of examination by which the presence of a local spinal lesion may be identified has been described. When spinal or back symptoms exist in the absence of a local lesion, the psychogenic nature of the illness may become quite clear on examination, as in Case 5 and in conversion hysteria. In other cases, though the diagnostic evidence strongly suggests psychogenesis, opportunity is not afforded by the patient for sufficient psychiatric investigation and treatment of the relevant factors, even though he may lose his symptoms (as in Case 4) during treatment essentially acting by suggestion.

The same event may give rise to both physical and psychiatric sequelae: this is, of course, very well known—for example, after head injury and when compensation is in the balance. Excluding such cases, we find true co-genetic physical and psychiatric symptoms to be uncommon when the pain is in the trunk. While Case 4 might well have been an example of this in the early stages of her illness, the physical component had undoubtedly all but vanished at the time she came under our care. Case 6, however, provides an excellent example of co-genesis, which, as will be noticed, occurred in a patient who later experienced a psychotic episode. The history of the treatment of this case demonstrates the well-known theme that the cure may promise to be, or may be, worse than the disease.

Case 1

A married man (a schizoid psychopath) aged 36, with three children and a much-involved emotional life, had at the age of 34 received treatment by electroplexy for a persistent intercurrent depressive episode, which thereupon resolved completely. Now, as a result of further emotional stress, he had again become depressed, although much less so, and was again referred for electroplexy. At the time of his attendance for the first treatment of the second course it was noticed that he limped a little. On questioning he admitted to pain in the left leg which had been present on and off for three months, for which he had been unsuccessfully treated by an osteopath. The pain had become very much worse during the preceding two days. A slipped disk was suspected and electroplexy therefore withheld for fear of increased displacement during the convulsion. On examination a pulpy protrusion at the fourth lumbar level (with limitation of straight-leg raising and diminution of the ankle-jerk) was diagnosed. Treatment by traction brought about reduction. During the period of this treatment the turbulence of his emotional life quietened, and his depression resolved without further treatment.

Comment.—This case illustrates the intercurrent spinal disorder, with the matter-of-fact attitude on the part of the patient, who would not spontaneously have mentioned his pain. The resolution of his depression is to be related to the events in his personal life and not to the spinal traction!

Case 2

A spinster schoolmistress aged 43 had suffered severely for four years from hysteria. This was manifested in symptoms of spasm affecting the gullet, bladder, and bowels; dermatographia; choreiform movements; various disorders of gait; pains in the back and head; fugue states. The syndrome occurred in bouts, usually in the vacations, the patient otherwise maintaining a keen, active, and efficient grasp of her job. Since adolescence, when she had had "chorea," she had been prone, on occasion, to bouts of illness with various selections of symptoms from the above-mentioned group. Her two sisters were very "nervous," one apparently pre-psychotic.

A few months after she came under our care she complained of severe backache. This she was able to locate below the shoulder-blade to the left of the spine, but would on no account allow palpation of the part because of the "extreme tenderness." At the time she was in a mild fugue state. The history was that the pain first came on when she was pushing up a large window with a pole, and had recently become worse when, travelling by car, she had, on a bumpy road, turned her head to look backwards. As soon as her mental state allowed examination of the spinal movements, she was seen for assessment of the possibility of a spinal lesion.

In spite of manifest exaggeration, clinical examination of the trunk disclosed the pattern of movements characterizing a left-sided mid-thoracic disk lesion, but she was not able to bear the touch of a finger-tip on the skin of her back. Hence manipulative reduction was carried out (somewhat unwillingly) under anaesthesia and full reduction secured. The result was immediate cessation of the pain at the posterior thorax, but the clouded consciousness persisted for a while. A year later this pain returned as the patient fell, grasping for a door jamb in an attempt to save herself. On this occasion she was in a less disordered emotional state, and consequently could permit manipulation without anaesthesia, which was again successful.

Comment.—This case illustrates the alternative reaction to the intercurrent physical condition (in contrast to Cases 1 and 3). In this instance a severely disordered hysteric over-reacted markedly to the lesion. When it was possible to discount the patient's *reaction* to her pain, the history and her description of its effects were typical of a spinal lesion, which was treated in its own right. The pattern of the neurosis remained unchanged.

Case 3

A married woman aged 33 who had had a miscarriage nine years earlier and who, since this event, had remained infertile and suffered from a chronic depressive state, was on the last account submitted to electroplexy. Her personality was tense, anxious, and dependent, and the psychiatric past history indicated a disposition to depressive bouts with phobic anxieties and bodily preoccupation, though earlier these had been milder and less sustained. Electroplexy induced a satisfactory improvement in the psychiatric state, but at the second treatment the patient complained of pain in the back. *X*-ray examination showed no fracture. Clinical examination suggested a disk lesion at about the fourth thoracic level. She quite cheerfully accepted her pain and continued with electroplexy. After this was completed, traction proved successful in abolishing the thoracic pain.

Comment.—This case illustrates clearly the intercurrent (iatrogenic) local lesion, and it was noticeable that the patient treated the pain in a most realistic manner—that is, quite differently from her attitude to her psychogenic symptoms.

Case 4

An ex-nurse, married seven years, had, since the birth of her child two and a half years earlier, suffered from pain in the right thigh and buttock, such that she held herself lop-sided. After four months she was put in a plaster jacket, which so increased the pain that it had to be removed eight hours later. After another four months, laminectomy was performed, but nothing abnormal was found. For five weeks she remained free from pain; then it returned, and persisted until coming under our care (fifteen months). She stated that she always woke comfortable and straight, pain and deformity increasing as the day wore on.

She sidled into the room, dipping on her right leg—quite a different gait from the limp of a patient with sciatica. Her lumbar spine was held vertically; her thoracic spine deviated to the right and the neck deviated grossly in the same direction. Examination of the trunk and lower limbs elicited the inconsistent responses that characterize psychogenic pain, but straight-leg raising on the right, though of full range, was painful at the extreme and that ankle-jerk was sluggish. It seemed, therefore, that a slight residual organic lesion existed. After a month's treatment by daily traction she stated that her back and limb no longer hurt. Her gait and posture had improved, but were by no means normal, in spite of daily training by a physiotherapist.

Psychological investigation revealed that she had been, socially, a very active and outgoing person, and had continued her nursing career until the middle months of her pregnancy. The onset of the pain in the leg and the subsequent operation disorganized her life and made it impossible for her to enjoy sports and dancing as she had done. She was able to maintain much less contact with her friends. There was little doubt that the patient was almost aware of the hysterical exploitation of her illness. Although she averred that she wished "to do everything to get well," she declined psychological treatment and put her hopes in physiotherapy, which was indeed bringing about a very rapid amelioration of her symptoms, although it was aimed only at stretching her hysterically fixed spine. In the patient's own words, "Now that something is being done, I am sure I will get well."

This patient denied any ambivalence with regard to the birth or rearing of her child, although the causative conflict was probably centred about the change in the pattern of her life consequent upon maternity.

Comment.—This case illustrates the extreme neurotic (hysterical) elaboration of a minor physical symptom, and may be regarded as predominantly hysterical.

Case 5

A woman aged 41, married nineteen years and childless, had been seen on two occasions at a year's interval on account of severe pain all over the back for three years. She had been in and out of several hospitals. Examination revealed the incongruous responses typical of psychogenic pain, and no local lesion of the moving parts was detectable anywhere. Psychiatric examination was advised.

The symptom picture suggested either a depressively coloured anxiety state or masked depression, and included spinal and generalized vague aches and pain, fatigue, depression, and irritability. Anxiety was manifest, both generalized and specific with regard to marital and domestic matters.

Significant points in the case history were: the mother suffered a psychosis on the death of the patient's father when she (the patient), the youngest of the family, was 2 years old. In consequence she was reared by a kindly aunt, who died six years later. Thereafter the patient was very unhappy, always sensitive, diffident, and lacking robust health or outlook. At 23—that is, one year after marriage—tuberculosis of the spine was misdiagnosed and treated by rest in bed for eighteen months. The marriage had been frictionful on several counts. (1) The mother-in-law, neurotic and elderly, shared the home for the first seventeen years of the marriage. (2) The husband, now aged 50, had suffered with a peptic ulcer for thirty years, and was a tense irritable man. (3) The sexual relations were impaired by ejaculatio praecox and frigidity. Furthermore, while the patient desired children and had sought help for her infertility, her husband refused to co-operate. Two years before she came under our care she had suffered from a vague illness with pain in the spine and body, mild depression, and marked anxiety with sleeplessness. Since then she had remained nervy and had not completely recovered. In recent months her condition had deteriorated. Her present spinal symptoms reminded her of her past "tuberculous" illness.

A narco-exploratory session was decided upon in order to establish the psychiatric diagnosis, but before this could be done the patient, after discussing matters with her husband, learned that he would on no account submit to an examination regarding his fertility and that, while he would welcome a daughter, he had had a lifelong fear that a son would destroy his marital peace. The decision to adopt a daughter resolved both the situation and the patient's symptoms.

Comment.—This case well illustrates the purely psychiatric illness presenting with purely physical symptoms.

Case 6

A single woman aged 46 complained of a rhythmic tic of the left eyebrow involving the left side of her face and neck and at times spreading to the right eyebrow. In addition

she complained of pain in the back between the shoulder blades, to the right of the spine. These symptoms had their onset some three years earlier, when, meeting the unexpected advances of an old acquaintance, she jerked her head and body violently backwards to avoid being kissed. At this moment something "snapped" in her back, audible to both of them, and local pain was felt at once. On waking next morning her face was twitching. The gentleman in question had a tic of one side of his face.

A diagnosis of co-genetic hysterical facial tic and local spinal lesion was made, and, as the patient was convinced of the organic nature of her tic, which she adamantly regarded as a physical consequence of the pain in her back, psychotherapy was postponed and the spinal condition treated first.

Examination showed that the patient was twitching all over, but principally on the left side of her face. Her replies when the moving parts of the neck, scapulae, upper limbs, and thorax were tested were perfectly consistent, and pointed to a thoracic disk lesion at the fifth level. Manipulative reduction was carried out, and when she attended two days later all movements were of full range and painless. This somatic relief had not affected her tic.

Thus the first response to treatment was loss of all symptoms in the back, but some months later a throbbing backache, synchronous with the pulse, developed. This, however, did not interfere with physical activity such as gardening and golf, as had the original symptoms. Psychotherapy, initially by means of narco-analysis and later by means of hypnosis, brought about subjective improvement only.

The patient, whose mother and sister were psychotic, had herself experienced a psychotic episode (for which she was treated by electroplexy in a mental hospital) one year or so after the traumatic incident. In spite of this history, but cautiously in view of it, hypnosis was undertaken in an attempt to suppress the facial tic. After some difficulty she was put into full trance and the facial tic was reduced and then abolished by direct suggestion. (Narcoanalysis had already afforded an adequate review of her problem, with apparently sufficient abreaction.) The improvement was transient, being followed by worsening and change in character of the spinal symptoms, which now included sensations of vibration, together with a return and spread of the facial tic. Psychotherapy was terminated.

Comment.—It would appear in this case that, not only did physical and psychoneurotic symptoms follow the same trauma, but when the later developing psychosis was relieved by electroplexy the neurotic symptoms served as channels of expression of residual psychic tension. Interference proved not devoid of danger, for, although physical treatment could relieve the local physical lesion, this was reactivated psychogenically.

Conclusions and Summary

Patients suffering from psychiatric illness may also suffer from local lesions in the moving parts of the body. Owing to the prominence of the psychogenic symptoms, the existence of the organic lesion may be overlooked or ignored. We have considered the problem of pain in the back as illustrative of this general thesis.

A system of examination is described which permits satisfactory differentiation of local lesions from psychogenic dysfunction.

The relationship between the physical lesion and the psychiatric state may be adventitious; but it may, as in one case cited, be caused by the physical aspect of the situation, which also provided the psychic trauma (Case 6).

The symptoms due to organic lesions can be differentiated from the rest of the symptom picture and treatment of the local lesion is often successful.

Patients suffering from psychiatric illness alone may present with symptoms relating to the moving parts of the body. They may respond to treatment directed to the psychiatric disability.

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PYRIMETHAMINE (DARAPRIM) AS A PROPHYLACTIC AGENT AGAINST A WEST AFRICAN STRAIN OF P. FALCIPARUM

BY

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Goodwin (1952) recorded his personal experience of pyrimethamine in the prophylaxis of malaria during a visit to equatorial Africa extending over a period of one year. Towards the close of the tour, while taking 5 mg. of the drug daily, he allowed himself to be bitten by four *Anopheles gambiae* which had fed on patients with gametocytes of *Plasmodium falciparum* in the peripheral blood, and in which sporozoites were subsequently demonstrated in the salivary glands. He concluded that in his case a daily dose of 5 mg. of pyrimethamine had proved a satisfactory suppressant of this strain of the parasite. So far as we are aware, there is no other published record relating to the prophylaxis of falciparum malaria by this drug in non-immune subjects.

Present Investigation

The object of the investigations here recorded was to ascertain whether a weekly dose of 25 mg. of pyrimethamine is sufficient to prevent an attack of falciparum malaria in a non-immune subject. The strain of parasite used was obtained in January, 1953, from an African child resident in Ilaro, a township about 50 miles distant from Lagos, Nigeria. Blood from this child was inoculated intramuscularly into a patient suffering from neurosyphilis. Subinoculations were later made into two other neurosyphilitic patients. All three developed overt malarial attacks, but in only one case were gametocytes produced in sufficient numbers in the peripheral blood for satisfactory infection of a batch of mosquitoes.

The mosquitoes used for transmission were *A. stephensi* (Type), a colony of which was established at Horton during the winter of 1947–8 from specimens imported by air from the Malaria Institute of India, Delhi. A batch of about 700 insects was allowed to feed on the gametocyte carrier.

The subjects of the prophylactic trial were 14 patients in Horton Hospital, two of whom had previously undergone malaria therapy for neurosyphilis with *P. vivax*. None of the others had any history of malarial infection.

They were arranged in seven pairs, each pair receiving the weekly dose of 25 mg. of pyrimethamine on a different day of the week (see Table). The first pair (A and H) took

their first dose on Day 1, the last (G and N) on Day 7. Throughout the trial every dose of the drug was personally administered by one of us.

The first infection was on Day 8, when 10 to 12 mosquitoes from the infective batch were applied to each subject. It was planned to examine the salivary glands of the mosquitoes which had fed on each subject serially until one was found positive. As it turned out, the first mosquito dissected was found infected in 12 cases, and the second in the two others. All infections were heavy. It was thus established that each subject actually received a dose of sporozoites.

During the trial each subject was exposed to the bites of 10 to 12 mosquitoes from the same batch on five occasions at intervals of three or four days. Routine dissections showed that salivary-gland infections continued to be heavy during the first three feedings, after which they began to diminish in intensity.

The Table shows that under this schedule the infections were distributed in such a manner as to cover all possible intervals between the taking of the drug and the infective bite on each occasion of feeding.

It was unfortunately not possible to infect a further batch of mosquitoes, and therefore the experiment was terminated after the fifth feeding. At this stage the seven pairs of subjects were split up, one of each pair receiving a single dose of pyrimethamine after his last exposure to infection, the others two doses.

A "control" was provided by a patient awaiting malaria therapy for neurosyphilis, who was infected from the same batch of mosquitoes on Day 9. Parasites were found in the peripheral blood on the seventh day after infection, and a febrile attack developed two days later.

Result

One of the subjects developed an abscess in the region of the right knee early in the trial, and had a temperature of 102° F. (38.9° C.) on the fourth day after the first feeding. He was treated with penicillin and the abscess was opened and drained, after which the temperature fell to normal. His blood was examined repeatedly, but no parasites were found. In any case, a temperature of 102° F. (38.9° C.) on the fourth day after exposure to infection could scarcely have been due to malaria.

One other subject had a temperature of 99° F. (37.2° C.) on the eleventh day after the first feed. The temperature had fallen to normal four hours later and there was no further rise. No parasites were found at any time in the peripheral blood.

There were no other incidents during the trial, and there was no evidence of any injurious side-effects. Protection against malarial attack under the conditions of the experiment was thus complete.

Discussion

The results recorded above indicate that pyrimethamine in a weekly dosage of 25 mg. is highly effective in preventing an overt malarial attack in subjects exposed to repeated infection with this strain of *P. falciparum*.

As to the mechanism by which this effect is brought about, the work of Archibald (1951), McGregor and Smith (1952), Vincke (1952) in West Africa, of Avery Jones (1952) in East Africa, and of Wilson and Edeson (1953) in Malaya has shown that this drug has a definite action against the asexual erythrocytic forms of *P. falciparum*, although in some instances, notably in Malaya, this action was considered too slow to warrant its use for routine therapeutic purposes.

From a study of the Table summarizing our results, it appears that pyrimethamine acts also on the pre-erythrocytic forms of the parasite and that it is therefore a true causal prophylactic of falciparum malaria.

As to the practical application of the findings recorded, pyrimethamine in this dosage seems likely to prove an effective and economical agent for the prevention of malaria among populations under disciplinary control, provided it can be ensured that the weekly dose is actually taken with unfailing regularity; for instance, in the case of a labour force paid on a weekly basis, where the drug can conveniently be administered at the time when wages are distributed.

For private individuals and officials or for populations not under disciplinary control, we do not consider that a weekly dose of any antimalarial drug offers a sufficient margin of safety. Experience has shown how easy it is for those on a daily dose regime to miss taking the drug, particularly in times of stress, and the risk is all the greater when the prescribed interval is as long as seven days.

We believe that in such circumstances the daily dose of 5 mg. of pyrimethamine adopted by Goodwin (1952) for his personal protection offers a better prospect of success, provided that its efficacy is confirmed by more extended field trials.

Schedule of Dosing with Pyrimethamine and Infection by Mosquito Bite

Days:	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35
A		p						x			x				x			x			x															
								p							p							p														
B			p					x			x				x			x			x														
									p							p								p												
C				p				x			x				x			x			x														
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D					p			x			x				x			x			x					p									
											p							p																		
E						p		x			x				x			x			x						p								
												p							p																	
F							p	x			x			p	x			x			x							p								
G								x			x				x			x			x								p							
							p							p							p															
H		p						x			x				x			x			x														
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I			p					x			x				x			x			x														
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J				p				x			x				x			x			x														
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K					p			x			x				x			x			x					p									
											p							p																		
L						p		x			x				x			x			x						p								
												p							p																	
M							p	x			x				x			x			x							p								
												p							p																	
N								x			x				x			x			x								p							
							p							p							p															

p=Pyrimethamine 25 mg. x=Infected by mosquito bite.

Summary

Pyrimethamine administered weekly in a dosage of 25 mg. afforded complete protection against overt malarial attack in a group of 14 non-immune subjects repeatedly exposed to mosquito infection by a West African strain of *Plasmodium falciparum*.

The action appears to be that of a true causal prophylactic against this species of parasite.

We wish to express our thanks to Dr. J. H. Watkin, physician-superintendent, and the staff of Horton Hospital for their co-operation, and to Dr. L. J. Bruce-Chwatt for kindly supplying the strain of *P. falciparum* used in this investigation.

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PROCTALGIA FUGAX

BY

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From time to time mention is made, commonly in the correspondence columns of the weekly journals, of a symptom-complex which is becoming increasingly more widely known as "proctalgia fugax." This was the name given to it by Thaysen (1935). The condition had been earlier, although not so completely, documented, but his happy choice of a new, neat, apt, and usefully non-committal label seems likely to win for him an enduring place as its real discoverer. It should be admitted, however, that at least one English etymological purist of high repute quarrels with "proctalgia fugax" as an unacceptable Greek–Latin hybrid, and many persist in calling it "nocturnal proctalgia." However, more careful inquirers usually award pride of place in the history of the complaint to MacLennan, of Glasgow, who described it very adequately in 1917. Professor F. C. Pybus, however, drew my attention to a short but practical article by Dr. Myrtle, of Harrogate, in 1883. He was obviously fully aware of the existence of this symptomatic disorder, and had encountered it several times in what was, presumably, a well-to-do spa practice.

Sir Frederick Wallis (1909), a proctologist on the staff of Charing Cross and St. Mark's Hospitals at the beginning of the century, also recorded what must surely have been another example, as it occurred in a highly nervous young man who had gone off round the world to seek relief from the bouts of distressing rectal pain. Wallis claimed, however, that he found a local cause for the paroxysms in the existence of a submucous recess leading up from the crypts of Morgagni. It is true that he relieved the condition by excision of the track, but further perusal of his writings on rectal diseases makes it obvious that he had something of a bee in his bonnet concerning the significance of similar submucous tracks in the causation of obscure rectal and anal pain.

Professor Pybus, as a young house-surgeon in the Gordon Hospital in 1909, was several times confronted with this condition, and in 1910 he submitted for publication in the *British Medical Journal* the typescript of a most informative communication of what he elected to call "nocturnal rectalgia." Unfortunately it did not find editorial acceptance, and it has spent 40 years fading in an unremembered corner. I was privileged to study this article, as well as a large and most interesting correspondence on this topic with doctors up and down this country. It was the long interest which Professor Pybus has had in this complaint that led to my writing this paper.

Incidence

It is, I believe, significant that of the increasing number of letters on this subject in the weekly journals (for proctalgia fugax threatens to become almost a perennial) the majority describe the personal experience of doctors who are themselves unhappy sufferers. (No fewer than six out of Thaysen's (1936) ten patients were physicians.) This apparently high incidence in our profession can be explained in two different ways: (1) that doctors are in fact peculiarly subject to it, or (2) that the ailment is much more common than we suspect, but that as it causes no great disability it imposes a burden inconsequent enough to be endured in secret without seeking medical advice. I suspect that the second of these explanations is the more reasonable one, for the pain which is its most prominent feature is of short duration and commonly recurs only at widely spaced intervals. If the frequency with which we are consulted about this complaint is really an indication of its true incidence it must be rare indeed, for an eminent consultant like Ryle (1948) encountered only 25 cases in 22 years' experience as a gastro-enterologist in hospital and private practice. There may, however, be some justification for the first contention. It is certainly true that it seems to occur more often in the brain-worker, although whether we as a profession pretend to excel in or even to belong to such a group I should hesitate to decide. These considerations are dealt with under the heading of aetiology.

First, however, let me describe the features of this symptom (for it is no more than a symptom) as related partly by the relatively few sufferers encountered in my own experience, but mainly as now recorded so adequately and so graphically in the testimony of many doctor patients.

All are agreed that the male seems to suffer more commonly than does the female. The maximum incidence is in adult life, from 20 to 50, but many reports suggest that the trouble may begin even in early childhood ("Biologist," 1952). I know of no patient who was first afflicted in the later decades of life. It often is familial in its distribution, father or mother and several children being affected (C.G.E., 1931; Lynch, 1931; M.c.P.F., 1935; Hurst, 1943). That the cause may be other than genetic is suggested by the fact that it occurs equally often in father *and* mother as well as in one or more of their offspring (MacLennan, 1917; "Neuralgia," 1931). The possible significance of its occurrence in several members of the same family is commented on below.

Clinical Features

The condition is characterized by recurring paroxysms of rectal pain which have one very characteristic feature—namely, their curious predilection to occur in the early hours of the morning. They also occur by day, commonly in the late afternoon or evening, when they may be initiated by vague ill-defined premonitory symptoms such as cool perspiration ("Biologist," 1952). The pain at the outset, and that is most often on wakening, is no more than a mild discomfort. During the next few minutes, however, it increases steadily in intensity, persists for some time unchanged, and then gradually passes off to be succeeded by a feeling of great weariness which usually leads to a restful sleep. The whole cycle lasts for from only a few minutes to half an hour or even more. The period between attacks

may be long enough to make the sufferer believe that each succeeding episode must surely be his last. Usually they return at intervals of many weeks or of several months. They may occur during a lifetime (Bett, 1952), but generally seem to diminish in frequency as the years roll on and even to abate completely in late middle or old age (Tidy, 1952).

As to the quality of the pain, sufferers have variously described it, but perhaps it is most often said to be cramping, gnawing, or even grinding, and always unremitting. But there are many more vivid accounts: "Like a sharp object held up at the recto-sigmoid"; "As if the rectum were being squeezed in a vice"; "Like a wire tied tightly round the bowel"; "Like a small ball expanding slowly." Perhaps none described it with more feeling than did the doctor who wrote of the "dull, throbbing, riving, tearing, sickening pain comparable to nothing in earth—one feels as though a big hard stone in the rectum was wanting to get out." Or maybe even he is outdone by the patient who feels that he "is being held very tightly by his rectum and is unable to escape" (Murray, 1951). However, it is only the severest bouts which merit such descriptions, and the attacks vary greatly in their intensity, from a slight discomfort, which can, by day, be endured with activity unimpaired, to the most gripping paroxysms culminating in a cold perspiration and often in syncope. On one point, however, all agree—namely, that the pain seems to originate not in the anus or in the anal canal but at a much higher level, deeply inside the pelvis. Although the exact site of the pain varies from one patient to the next, it tends to recur in any one individual always in precisely the same place; in different attacks it may be constant neither in its intensity nor in its duration.

There are few, if any, associated symptoms, apart from a not uncommon desire, but often a distressing inability, to empty the bowel or to pass flatus. During the height of the severer paroxysms the patient feels quite unable even to move in bed, and any desire to leave it is often suppressed for fear of inducing thereby a syncopal attack.

Of physical signs there are none, and the condition occurs usually in people who are otherwise apparently healthy. I can find only one record of a sigmoidoscopic examination having been carried out during a spasm. This must have been a unique experience, not as yet enjoyed by the many afflicted among our colleagues who have done their best to discover the truth by self-examination of the rectum. Spasm of the external sphincter has seldom been reported, and, although muscular contraction at a higher level is said to have been found on some occasions, one questions the ability of even the most dextrous accurately to assess the degree of muscle tone of his own ano-rectal ring. In any event, it is difficult for the patient himself to reach with his own finger as high as the point where sensation suggests the pain to be.

Bolen (1943), who passed the sigmoidoscope during an attack in a man of 60, reported a reddened swollen mucosa with prominent vessels. Pressure with the beak of the instrument at the central point of the levator caused mild spasm. Difficulty was had in negotiating the recto-sigmoid junction, and gas escaped as soon as the corner had been turned. But then none of these is really an uncommon sigmoidoscopic finding, and as an isolated observation it is doubtful if they merit more than to be noticed in passing. The evidence of most patients does, however, suggest that the discomfort is caused by a sustained spasm of the musculature of the rectum, although which component is mainly affected is a matter of guess-work.

Diagnosis

One should always show a natural reluctance to make a symptomatic diagnosis, and that of proctalgia fugax must be hazarded only with the greatest caution. Even when the story is unfolded, typical in its completeness, the most searching local examination should be made to ensure that there is no other cause for the pain. The spasmodic and often deep-seated and unremitting pain of a fissure is well known: of all the causes of rectal pain this is the one which most urgently requires careful exclusion. Other less common causes of pain, such as submucous abscess and vesiculitis, must also be borne in mind.

There is scant evidence to support the belief that rectal crises occur in tabes (Ryle, 1942), but, in spite of any scepticism there may be on this score, the pupils and the knee reflexes should be examined in every case.

Aetiology

As to the causation of this complaint there is no reliable evidence and for the most part speculation is rife. Many different happenings are alleged to precipitate attacks, exposure to cold, as in so many conditions, being blamed very often (Myrtle, 1883; "Septuagenarian," 1935). Constipation or the failure adequately to empty the bowel of small scybala before retiring may also be held responsible, but the pain seldom occurs with a full rectum (Pybus, 1952, personal communication). More often it seems to be precipitated by sexual intercourse, by masturbation (Blyth, 1935), or by nocturnal emission. Cessation of the practice of coitus interruptus was followed by complete remission in at least one instance (McEwan, 1935). The attacks are commonly associated with priapism.

The disorder is no doubt primarily a psychosomatic disturbance, a psychoneurosis of which it is the sole physical manifestation (Abrahams, 1935; Murray, 1951). The occurrence by day is, on the admission of many, largely determined by times of stress and anxiety, when things will not go right, when the mind is very weary, when work is irksome, or when, try as he will, the worrying patient cannot forget life's problems and injustices and seeks in vain some relieving relaxation. The malady afflicts those whom the layman would label "highly strung." When work is congenial and interesting, when the patient is at peace with himself and the world, that is no time for the paroxysms of proctalgia ("Biologist," 1952). Extreme physical tiredness may also often seem to be responsible (Sheppard, 1952), as may sexual excess.

The nocturnal attacks are similarly precipitated by a worrying, unsettling, and profoundly frustrating dream or nightmare, the moment of wakening being associated with considerable mental distress; alternatively, the content of the dream may be erotic in character.

Not every patient will admit to an association with times of tension and worry, and more ordinary alleged precipitating causes include straining at stool, the taking of a hot bath, infestation by threadworms (Lynch, 1931), or erythromelalgia (Carter, 1935). It is doubtful, however, if any of these is important as a primary factor in the causation of this somewhat obscure malady. Proctalgia seems to increase in frequency as the social scale is ascended, always accepting that the number of patients who seek advice is an index of its real incidence. But that is no more than one might reasonably expect from a trouble which is in some way related to fatigue, mental as well as physical; and this is surely where one must look, at least in part, for the high incidence in medical men.

As Gabriel (1948) points out, the condition, again as it occurs among the more responsible and intelligent citizens, is aggravated by a fear of cancer.

The vague premonitory signs sometimes reported suggest an aura, followed as it is by a "seizure" and by a phase of tiredness, and these have led some to believe the condition to be an epileptic manifestation, a belief to which the frequency of a family history lends some support. Only MacLennan (1917) and Carlill (1935) have put this forward as a really serious suggestion. The high incidence of this symptom in several members of a family (father, mother, and children alike) is more reasonably explained as being the result of identification with other people who have had similar, or even dissimilar, rectal disease (Murray, 1951).

Treatment

The most effective method of treatment is the taking of food. Immediate relief is the rule (Pybus, 1946; Bett, 1952), and even the drinking of a glass of cold water may be enough to do the trick (Hughes, 1952). It is reasonable to assume that the initiation of the gastro-colic reflex inhibits the painful muscle spasm. No doubt the same result can be achieved in other ways, but the use of volatile antispasmodics, of which chloroform and amyl nitrite have been most popular, has been in my experience uniformly unsuccessful. Perhaps the spasm can be relieved by the conscious search for mental relaxation, but this is a process which even at the best of times is exceeding difficult to initiate: it would seem more reasonable to seek a solution below the conscious level, by simply taking a biscuit and a glass of milk.

The variety of the measures which have afforded relief in this complaint gives further support to the belief that it is a visceral neurosis, although it is admitted that this is a common enough happening in any complaint which is naturally self-resolving and of short duration. Each sufferer has learned from his own experience some manœuvre which seems to help. For some the application of warmth, whether by clothing or by a hot-water bottle, may be enough; others get respite from a change in position, to the genu-pectoral (Bull, 1952), or to the squatting (Smith, 1935), or to sitting on the very edge of a chair, or even to a sitting-up position in bed. The passage of flatus may ease the pain almost immediately, as will the discharge of any particulate faecal material, however small in amount: it is likely that each only signals the relaxation of muscle spasm and the end of an attack. Commonly, the patient can expel nothing at all from the rectum, and the effort of ineffectual straining may only intensify and prolong the spasm.

Most of the other lines of treatment are largely impracticable—such as the passing of a rectal catheter, or even the giving of a small enema, warm or cold, water or oil, or even air alone. It seems likely that any success in such manœuvres results from engaging the attention and by arousing interest, curiosity, or expectation.

Summary

Proctalgia fugax is a condition characterized by recurring attacks of pain deeply inside the rectum. The pain follows a definite pattern, and no local cause can be found to account for it. It has certain features which suggest that it is due to a sustained muscle spasm. It can be relieved most effectively by the immediate taking of food or drink.

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ADRENALINE CREAM

AN ASSESSMENT OF ITS VALUE IN THE RHEUMATIC DISORDERS

BY

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Adrenaline cream seems to have been used first in the treatment of rheumatic conditions by Moss in 1949 on the grounds that it might be absorbed sufficiently to cause vasodilatation in muscle and thus aid massage in patients suffering from fibrositis for which a causal "vasomotor disequilibrium" had been postulated. He claimed that all patients except those with early osteoarthritis improved, and that most were symptom-free after a few treatments. As no comparison was made with patients receiving simple massage or massage with an unmedicated cream it is not possible to assess the effect of the adrenaline component from Moss's results.

The effect of adrenaline cream was further studied by Howell (1950) in 90 patients with "fibrositis secondary to rheumatoid or osteoarthritis." In comparable groups of 20 patients there was relief of pain for more than four hours in 77% of patients massaged with adrenaline cream and in 20% of those receiving a simple cream—an apparently significant difference.

Bywaters (1951) studied 39 patients suffering from conditions associated with deep pain of symmetrical distribution. Adrenaline cream was rubbed into one side and a plain cream into the other. Improvement occurred in 29% of trials with adrenaline cream and 25% of controls. Relief was complete in 17% of 283 trials with adrenaline cream and 13% of 289 with plain cream. These differences are not significant, nor was there any significant difference in the duration of relief; it was therefore concluded that there was little difference between the effects of the two creams when administered in this way.

Present Study

The present trial was undertaken as part of a study of the value of physiotherapeutic procedures in the rheumatic diseases, and was carried out at a clinic for the treatment of rheumatism in miners. The distribution of rheumatic disorders in patients used in this study is indicated in Table II.

Two separate investigations were made: (1) a study of palliation, and (2) an investigation of recovery times.

Palliation was studied in two stages. In the first stage, carried out on a group of 65 patients, comparison was made between two creams—one containing 0.1% adrenaline, the other a simple cream base. These were so labelled that the identity of the adrenaline-containing cream was unknown either to the physician or to the physiotherapy staff, and were assigned alternatively to new patients attending. When the patient had received treatment thrice weekly for two weeks the palliative effect was assessed, and he was then transferred to the other treatment, which in turn was assessed on completion of the sixth treatment. In the second stage of the investigation, carried out on another group of 60 patients, adrenaline cream was compared with dry massage and with no massage, each patient being thus studied for three consecutive periods, the initial treatment being decided as before by a rota. As in the first stage, these treatments were given over a period of two weeks

before the assessment was made. In some patients the symptoms did not persist long enough for more than one or two treatments to be assessed. Other physiotherapeutic procedures (short-wave diathermy, radiant heat, etc.) remained unchanged throughout the period of stay.

Assessment was made of the degree and duration of relief, and was by questionary. The results are shown in Table I. Patients had no difficulty in deciding whether relief was complete or partial or was non-existent, but could not always be certain of the duration of relief. Where doubt existed they were asked to state whether relief was for more or less than five hours, and this was used in the composite assessment, shown in the last line of the table.

TABLE I.—*Palliative Effect of Massage with and Without Adrenaline Cream*

	Controls			Massage with Adrenaline Cream
	No Massage	Dry Massage	Massage with Simple Cream	
Total assessments ..	51	45	45	101
Complete relief ..	5 (10%) S	8 (18%)	6 (13%) S	26 (26%) S
Partial relief ..	35 (69%)	35 (78%)	33 (73%)	66 (65%)
No change	11 (22%) S	2 (4%) S	4 (9%) NS	6 (6%)
Worse	0 (0%)	0 (0%)	2 (4%)	3 (3%)
Duration of relief (mean)	14 hours	17 hours	9 hours	14 hours
*Composite score ..	1·4	1·9	1·5	2·0

* Mean figure based on following points system: −1=aggravation; 0=no change; 1=partial relief for less than 5 hours; 2=partial relief for more than 5 hours, 3=complete relief for less than 5 hours, 4=complete relief for more than 5 hours.

S indicates that the difference is statistically significant—that is, the observed difference is more than twice its standard error. NS=Not significant.

The data in this table refer to the treatment assessments and not to the patients, since in most instances patients had two or more treatments. Each assessment is an average of the effect of six treatments.

Results

A greater proportion of those receiving dry massage showed complete relief than of those not receiving massage, and fewer showed no relief of pain, the latter point being significant, so that dry massage is evidently capable of augmenting the palliative effect of other therapeutic procedures. Massage with simple cream was less effective than dry massage, and the group treated in this way did not differ significantly from the control group, so that a lubricant of this type apparently abolished the beneficial effect of massage. Adrenaline cream, on the other hand, produced complete relief in a significantly greater proportion of patients than simple cream, and the difference between the adrenaline-cream and control groups is highly significant. A few of those on adrenaline cream, however, complained of a temporary worsening of the pain, as indeed did those on the other types of cream. The duration of relief was not greatly affected by any of these procedures, though dry massage appeared to give rather more relief than other methods. The results are summed up in the composite score, which shows that dry massage and massage with adrenaline cream produce a similar degree of palliation, but simple cream is ineffective.

The effect of adrenaline cream on recovery was investigated by a separate investigation. Alternate patients were treated with adrenaline cream throughout and until medical finality was reached, the remainder being maintained on massage with a simple cream in the same way. Medical finality was defined as recovery of such degree that treatment was no longer required, or, alternatively, there had been no improvement over a period of four consecutive weeks. All patients were put on to a rota of other physiotherapeutic measures (short-wave diathermy, radiant heat, etc.), and these were changed in strict rotation at weekly intervals in order to avoid error from the effect which such treatments might have on recovery times.

The results are shown in Table II. Altogether 64 patients were studied, 32 in each group. Both groups were closely similar: all were males; the average age was 46 in the treated group and 50 in the controls; the mean duration of symptoms was identical and the diagnostic spectrum closely similar. Rather more of those in the control group were incapacitated for work, so that the control group is, if anything, of rather greater severity.

TABLE II.—*Effect of Adrenaline Cream on the Outcome of Rheumatic Disease*

	Adrenaline Cream	Simple Cream
Total patients	32	32
Average age	46	50
Before treatment:		
Diagnosis:		
Disk degeneration	8	8
Disk prolapse	2	2
Osteoarthritis	7	6
Rheumatoid arthritis	2	2
Other defined rheumatic disorders ..	4	4
Undetermined rheumatic disorders ..	7	7
Neurosis	2	3
Off work	14	17
On light work	8	5
On full work	10	8
Retired	0	2
Average duration of symptoms in days	38	38
Results:		
Quiescent	7	7
Improved and discharged	14	13
Improved to a point, then stationary ..	1	1
Improved, still under treatment ..	0	1
Unchanged	7	7
Worse	0	0
Non-attendance, etc.	3	2
Returned to work	11	16
Stopped work	2	0
Not known	0	1
Average days to return to work ..	65	32
Average days' attendance at clinic (quiescent or improved and discharged cases)	105	85

The final outcome was identical, seven patients in each group losing all symptoms and signs, and 14 and 13 respectively improving to a point where treatment was no longer required. Seven in each group remained unchanged. Apart from one who could not be traced, all those in the control group returned to work, but of those receiving adrenaline cream, three failed to return to work and two who were originally at work had to stop. This effect on incapacity is significant, and is confirmed by the delay in return to work in those who ceased to be incapacitated. This takes twice as long in those receiving adrenaline cream and the duration of treatment is correspondingly increased.

Discussion

Any investigation of palliative action must of course depend on answers to questions, and is therefore subject to influences both by the ideas of the patient and by the attitude of the questioner. Moreover, in a study such as this the attitude of the masseur must also be taken into account. Since, however, the comparison of adrenaline and unmedicated cream was carried out blind, it is unlikely that any such factors could have influenced the results in this study. The similarity of our results to those obtained by Howell (1950) is also confirmatory. With dry massage a blind trial was not of course possible, and some doubt must therefore remain about the relative influence of physiological changes and suggestion. The question is, however, academic rather than practical, relief of pain being equally acceptable to the patient, however produced. From the point of view of palliation, therefore, no advantage seems to result from substituting adrenaline cream for the normal talcum powder of the masseur.

The mode of action of adrenaline cream is by no means clear. It has been ascribed to an increased blood supply to the painful muscles due to the vasodilatation produced by adrenaline in skeletal muscle, a result which might well be augmented by the mechanical effect of the massage, and possibly also by the vasoconstriction which the adrenaline produces in the skin vessels. This would result in the tissue temperature approximating to that of the blood instead of the rather lower temperature found normally in

the more superficial muscle groups. It is known from the experiments of Kellgren, McGowan, and Hughes (1948) that pain in such structures is related to the local temperature. Such an effect must presumably depend on absorption of adrenaline into the general circulation, as penetration to such tissues by direct spread would be unlikely. This would explain the identical relief felt on both sides when adrenaline is applied to only one half of the back (Bywaters, 1951).

The delay in recovery which, as our figures indicate, follows the use of adrenaline cream may be due to interference with the pain-defence mechanism. A similar effect on recovery times has been noted when procaine is injected repeatedly into a site of pain in muscle or connective tissue. Whether dry massage produces a similar delay is at present uncertain, but is under investigation.

Summary

Adrenaline cream applied locally in a number of rheumatic diseases gives greater relief than a simple cream. Dry massage also gives greater relief than massage with simple cream or no massage at all. No significant difference was noted between the effects of dry massage and massage with adrenaline cream.

Repeated application of adrenaline cream appears to delay recovery in rheumatic diseases.

We wish to thank Dr. J. H. Kellgren, Director of the Rheumatism Research Centre, for his encouragement and advice, and Messrs. D. Mawdsley, of Manchester, for supplies of unmedicated and adrenaline cream.

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SÉZARY'S RETICULOSIS WITH EXFOLIATIVE DERMATITIS*

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The original account of this condition is contained in an article by Sézary and Bouvrain (1938). Their patient, a woman of 58, presented as a case of mild pruritus of the trunk and limbs, which became steadily more severe and extensive and was followed in two or three months by the appearance of erythematous plaques on the affected area. Fine scales developed on these plaques, and they gradually increased in size to produce a generalized erythrodermia. Microscopical examination of her skin showed a considerable infiltration of the dermis. The infiltrate consisted of round or polygonal cells with a round or oval nucleus and an indistinct nucleolus. Repeated blood examinations gave a red-cell count which varied from 3,500,000 to 4,490,000 and a white count ranging from 6,000 to 14,400 per c.mm. The blood film showed from time to time the presence of an unusual type of giant cell in numbers varying from 2 to 56 per hundred white cells. These *cellules monstreuses*, 12 to 14 μ in diameter, contained a large nucleus surrounded by a thin band of cytoplasm. The nucleus varied in shape, was sometimes oval or occasionally bilobed, rectangular, or lanceolate. The bone marrow contained none of these cells. Sézary believed them to be of mesenchymatous origin, but had never previously seen any similar cells.

In the discussion following the presentation of this case Civatte stated that he had seen this type of cell on three occasions. The patients in whom it was found all ultimately developed cutaneous tumours, and Civatte was undecided whether they should be regarded as examples of atypical mycosis fungoids, Hodgkin's disease, or leucosarcoma. Two further cases (Sézary, Horowitz, and Maschas, 1938; Sézary and Bolgert, 1942) closely resembled the original one, as did a fourth reported by Baccaredda (1939). All these patients died in 18 to 40 months without developing cutaneous tumours. Sézary thought it probable that the condition was related to mycosis fungoides, but felt that no more definite opinion could be given until further evidence became available.

Case History

A retired clerk aged 67 had suffered from transient rashes on the arms and legs for 16 years. The rash would last a few weeks and then clear, leaving a few residual eczematous patches which caused him no discomfort. Within one or two months there would be an exacerbation. This state of affairs continued until March, 1949, when he developed an unusually severe attack, accompanied by oedema of the legs. He was admitted to Paddington Hospital on March 14, 1949. A few days later he developed a small ulcer on the right ankle. Three weeks after this his face became red and swollen. Within a week scaling developed on the face and was rapidly followed by a similar scaling eruption on the scalp and limbs. The trunk was later affected, but not so severely as the face and limbs. There was moderate itching and considerable burning of the skin. He had had "barber's rash" when aged 45, gastric ulcer when aged 50, and seborrhoeic dermatitis causing his admission to hospital on three occasions when aged 55. His mother's brother suffered from industrial dermatitis. One brother suffers from asthma and occasional eczema.

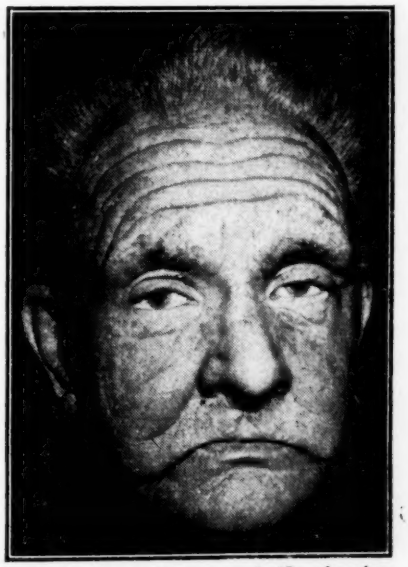

FIG. 1.—The patient, aged 67; showing oedema of skin, pigmentation, and pseudo-ptosis. The photograph is the copyright of the Royal Society of Medicine.

Examination showed him to be a small frail elderly man weighing 8 st. 12 oz. (51.1 kg.). His temperature ranged between 97 and 100° F. (36.1 and 37.8° C.), and pulse from 96 to 108. He was melancholy and apathetic. The skin of the face was thickened, and both eyelids were distended with oedema, which gave an appearance of ptosis and collected in pockets below the eyes (Fig. 1). There was considerable scaling over the face, scalp, and limbs. On the trunk the skin was thickened and covered with fine

*Part of a thesis submitted for the degree of M.D. Cambridge.

branny scales, larger on the arms and legs than on the abdomen. Superficial oedema obliterated the abdominal folds. There was no scaling in the axillae or groins. The whole skin was red; there was mottled brown pigmentation, particularly on the back and limbs. Many excoriation marks were seen on the legs, some weeping patches, and several superficial ulcers, all of which showed signs of healing. The hair was sparse, but the finger-nails and toe-nails were unaffected. The cervical, axillary, and inguinal glands were moderately enlarged. The patient was edentulous, the mucosa of the mouth was normal, and the tongue was unaffected. No abnormality was found on general examination. The spleen and liver were not palpable.

He was treated with an initial course of intramuscular injections of penicillin, 250,000 units six-hourly, and later with amphetamine, 10 mg. daily, and local applications of boric ointment.

While in hospital his skin condition remained substantially unchanged except for an increase in pigmentation. Six months after admission his liver became enlarged and

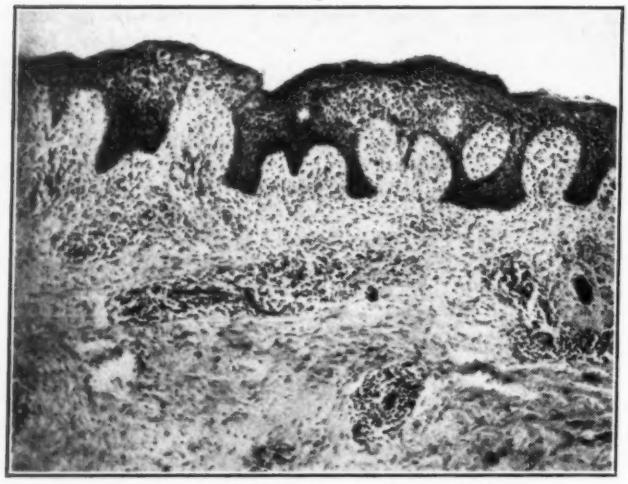

FIG. 2.—Biopsy of skin, showing dermal infiltration.

was palpable two fingerbreadths below the costal margin. About the same time he developed contractures of the legs, which were thought to have resulted from disuse, and a small trophic ulcer over the sacrum. He was discharged home in June, 1950. His condition remained unchanged until his death from cardiac failure in September, 1950, eighteen months from the onset of the disease. A post-mortem examination was not made.

Investigations.—A biopsy of the skin was made on August 4, 1949. The epidermis showed parakeratosis and acanthosis, with spongiosis, vesicle formation, and immigration of round cells. The upper third of the corium was oedematous and showed an increase of vessels and an infiltrate which was partly perivascular and partly diffuse (Fig. 2). The infiltrate itself was composed chiefly of round cells and a few histiocytes. *X*-ray examination of the chest showed no abnormality. The Wassermann reaction was negative. The urine showed no abnormalities. On November 29, 1949, serum protein was 6.9 g.%—albumin 3.9 g.%; globulin 3 g.%; albumin/globulin ratio 1.3/1.

Haematological Findings

Routine examination up to August, 1949, revealed a mild normochromic anaemia, haemoglobin 82–92% (11.4–13 g. per 100 ml.); a constant thrombocythaemia, platelets 730,000–820,000 per c.mm.; a constant leucocytosis, white blood cells 10,000–20,000 per c.mm. The differential white count varied considerably (see Table).

At this time large nucleated cells, numbering 1–2% of the total nucleated cells, were seen in the film of the peripheral blood. These cells, 15–25 μ in diameter, were irregularly ovoid in shape, and often drawn out into pseudo-

Date	W.B.C.	Polymorphs	Eos.	Baso.	Lymphs	Monos
4/5/49 ..	17,800	84	4	1	10	1
31/5/49 ..	18,800	51	6	1	32	10
14/7/49 ..	10,200	58	—	—	40	2
21/7/49 ..	16,000	84	—	—	15	1
27/7/49 ..	14,000	72	5	—	19	4
10/8/49 ..	16,800	50	4	—	44	2

podium-like processes. The rounded nucleus, occupying rather more than half the cell, showed a uniform open meshwork chromatin structure, a well-defined margin, and two or three variably distinct nucleoli. The delicately foamy and tenuous cytoplasm stained very faintly blue with Leishman, and sometimes contained many small azurophil granules. These large cells were clearly of reticulum type (Fig. 3). In a small proportion, convolution of the nucleus was pronounced and gave some resemblance to primitive monocytes. Following this initial observation these reticulum cells were seen in almost all subsequent films. The

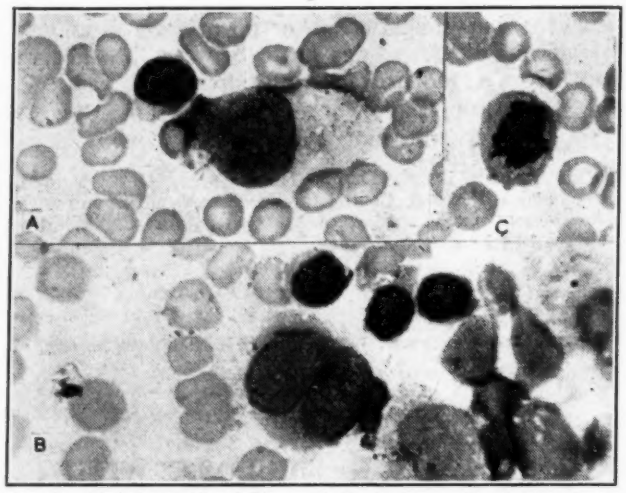

FIG. 3.—Peripheral blood film. (*a*) Reticulum cell, (*b*) binucleate reticulum cell, (*c*) mitosis in reticulum cell.

leucocytosis continued and at most examinations the number of reticulum cells seen was few. On two subsequent occasions, however, large numbers of these abnormal cells appeared in the peripheral blood and then disappeared after a few days. They were seen in venous as well as in capillary blood. These showers of reticulum cells were accompanied by an increase of lymphocytes and a decrease of polymorphs.

Leucocyte Counts.—December 14, 1949: W.B.C. 23,800 per c.mm. (polys 41%, eos. 2%, lymphs 48%, monos 9%). "There are numerous reticulum cells present, of the type previously described; many of the lymphocytes show primitive characters with nucleolar remnants." January 2: W.B.C. 21,200 (polys 68%, eos. 4%, lymphs 22%, monos 5%, baso. 1%). January 10: W.B.C. 17,800 (polys 29%, eos. 3%, lymphs 50%, monos 1%, reticulum cells 17%). "The film shows a remarkable picture; many mitoses are seen amongst the reticulum cells; many lymphocytes again show immature characters." January 21: W.B.C. 19,000 (polys 67%, lymphs 32%, monos 1%).

The mild anaemia slowly deteriorated to haemoglobin 75% (10.5 g. per 100 ml.) in October, 1949. No nucleated red blood cells were seen at any time in the peripheral blood and a sternal marrow puncture on November 5 showed normal cellularity and normal distribution of the nucleated cells.

The reticulum cells included haemocytoblasts 1%; myeloblasts 3%; promyelocytes 1%; neutrophil myelocytes 16.5%; eosinophil myelocytes 2%; metamyelocytes 24%; eosinophil metamyelocytes 1%; polymorphs 29.5%; eosinophils 1.5%; lymphocytes 5%; plasma cells 0.5%; pro-

erythroblasts nil; basophil normoblasts 2%; polychromatic normoblasts 9.5%; orthochromic normoblasts 3.5%.

Lymph-node Biopsy.—Dr. H. Haber reported: "The structure of the lymph node is changed, the follicles being atrophic and the sinuses showing a hyperplasia of reticulum cells which contain vacuoles and melanin. There is also an admixture of eosinophils demonstrable. Histological appearance of lipomelanic lymphadenopathy."

Discussion

The occasional association between a disturbance of the reticulo-endothelial system and generalized redness and scaling of the skin is well known. The original account of mycosis fungoides (Alibert, 1832) refers to a scaling pre-mycotic phase, the importance of which was later recognized by Brocq (1889). Under the title lymphodermia perniciosa a case was reported (Kaposi, 1885) in which there was exfoliative dermatitis with cutaneous tumours and a blood picture suggesting lymphatic leukaemia. There are many records of chronic erythrodermia associated with a clinical and haematological picture of leukaemia (Elsenberg, 1887; Riehl, 1892; Arndt, 1914; Ketron and Gay, 1923; Barney, 1928; MacCormac and Whitby, 1936). There was leukaemic infiltration of the dermis in most of these patients; a few (Sweitzer, 1916; Wise, 1917) showed cutaneous infiltration with a normal blood picture; and in one (Lutz, 1937) there was a leukaemic blood picture and a dermal infiltrate, but no post-mortem evidence of leukaemic changes elsewhere. Lutz therefore suggested that leukaemia might originate in the skin.

Exfoliative dermatitis has also been described with monocytic leukaemia (Montgomery and Watkins, 1938), Hodgkin's disease (Symmers, 1924; Miller, 1928; Wigley, 1937; Epstein and MacEachern, 1937), and giant follicular lymphadenopathy (Symmers, 1938; Combes and Bluefarb, 1941). In lymphoblastic erythrodermia (Sequeira and Panton, 1921) there was erythrodermia with lymphadenopathy and lymphocytosis, but no evidence of leukaemia.

Reviewing the four published cases of his *nouvelle reticulose*, Sézary (1949) described the following symptoms: intense itching of the skin and burning of the tongue and buccal mucosa, sensations of cold and sweating, but no impairment of the general health until the disease was well advanced. The skin was found to be red and pigmented, warm to the touch, and thickened, having a pasty consistency. There was oedema sufficient to produce puffiness of the eyelids, a leonine facies, obliteration of the normal abdominal folds, and swelling of the legs. The conjunctivae were often suffused. Two cases showed dystrophic changes of the nails. There was enlargement of the superficial lymph nodes in all cases, splenomegaly in two, and hepatomegaly in one.

Much of this detailed description might apply to any case of generalized exfoliative dermatitis. There are, however, several distinctive clinical features. Involvement of the mucosa is unusual in the more chronic cases, although it has been described in the acute scarlatiniform erythrodermia of Féréol. Some oedema of the legs is evident in most cases of exfoliative dermatitis, but gross oedema of the face and abdominal wall is rare. Injection of the conjunctivae is not uncommon in erythrodermia resulting from arsenic or phenobarbitone, but does not usually occur apart from this. The combination of scaling, pigmentation, oedema of the skin, and pseudo-ptosis gave a facies, illustrated by Sézary, which was remarkably reproduced in the present case.

In addition to these clinical features Sézary's cases showed particular haematological changes, including the appearances of *cellules monstreuses* in the peripheral blood. Sézary was unable to classify this cell, and the nearest approach he cared to make was "monocytoid." Most of the abnormal cells seen in the present case do not appear, from the published illustrations and Sézary's description, to be identical with his, although both are clearly primitive reticulum in type. A few cells, however, more closely resembled Sézary's *cellules monstreuses* in the convoluted character of the nucleus and clearer cytoplasm, and it is possible that they represent varying stages of development or activity of a common cell type. Sézary emphasized the intermittent flooding of the peripheral blood with these cells and the accompanying fall in the numbers of circulating polymorphs with an increase in lymphocytes. These features were also seen in the present case.

The clinical findings, the course of the disease, and the haematological picture described by Sézary are clearly reproduced in this case, and we have no hesitation in calling this a fifth example of Sézary's cutaneous reticulosis with erythrodermia. We feel, however, rather diffident in using the term "reticulosis" in this connexion. Insufficient consideration has been given in the past, in these so-called dermal reticuloses, to the point of view that the cellular features represent a non-specific response to the gross disorder in the dermis and epidermis which is not, at least to begin with, malignant in character. A similar consideration affects the so-called lipomelanic reticulosis of Pautrier and Woringer (1937), in which the changes in the superficial lymph nodes are now generally thought to be a non-specific reaction to the cutaneous disturbance. Until further evidence is available concerning the nature of the disease we suggest the noncommittal title of "exfoliative dermatitis with reticulaemia."

Summary

A case of exfoliative dermatitis in a patient who gave a long history of eczema is described. Large reticulum cells were found in the peripheral blood. The patient died without developing any of the characteristics of the known reticuloses. The clinical and haematological features were similar to those described by Sézary as a new cutaneous reticulosis, and the case is the first to be reported in this country.

We should like to thank Dr. J. E. M. Wigley, under whose care this patient was admitted, for permission to report this case.

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About 180 general practitioners are employed by the London County Council on a sessional basis. About 65 of these work in the school health service, and the remainder are employed at ante- and post-natal clinics, child welfare centres, vaccination and immunization clinics, and at dental clinics as anaesthetists. On an average these general practitioners attend two sessions a week each, and are responsible for about one-third of all the sessions worked under the National Health Service Act.

Medical Memorandum

Mephenesin in the Treatment of Tetanus

Since its introduction by Berger and Bradley (1946), "myanesin" (mephenesin) has been used with success to control muscle spasm in tetanus, usually by intravenous and intramuscular routes and more lately orally (Belfrage, 1947; Torrens *et al.*, 1948; Macdonald, 1949; Davison *et al.*, 1949; Godman and Adriani, 1949; Newhouse *et al.*, 1950). It alleviates muscle spasm by depressing spinal-cord reflexes and also depresses the function of the basal ganglia and brain stem (Stephen and Chandy, 1947; Schlesinger *et al.*, 1948; Gammon and Churchill, 1949). Unlike curare, mephenesin does not depress respiration and is possibly less likely to liberate histamine. A case of tetanus of moderate severity is here reported in which combined intravenous and oral administration gave satisfactory control of muscle spasm.

CASE REPORT

A housewife aged 62 was admitted to hospital with a provisional diagnosis of arthritis of the left temporo-mandibular joint. Her illness began ten days earlier with stiffness of the neck, pain in the left jaw joint, followed a week later by difficulty in swallowing. On admission the patient was suffering severe pain in the region of the left temporo-mandibular joint, which was aggravated by any movement of the jaw. She was afraid to talk and had taken practically nothing by mouth for three days. Movement of the jaw was extremely limited, the left masseter muscle was in strong spasm, the right masseter and the neck muscles were moderately hypertonic. There was an ulcer, 1 by 0.5 cm., with indurated edges on the inner surface of the left cheek. The pulse rate was 80, temperature 98.4° F. (36.9° C.), blood pressure 150/100 mm. Hg, and E.S.R. 19 mm. per hour. Radiographs showed no abnormality of the temporo-mandibular joints.

The severe pain persisted, little relief being afforded by aspirin, codeine, and injections of pethidine, 100 mg. Fluid was administered per rectum as the patient could swallow only with difficulty. By the fifth day after admission she was unable to take anything by mouth; attempts to swallow caused retching and spasm of the muscles of the jaw, neck, thorax, and abdomen. Examination revealed spasm of the masseters, more severe on the left, also spasm of the neck muscles, some degree of risus sardonicus, and hypertonic abdominal and leg muscles. Tendon reflexes were very brisk and there was bilateral poorly sustained ankle clonus. The patient was very apprehensive of any interference. A provisional diagnosis of tetanus was made on the fifth day and treatment was started with 200,000 units of antitetanic serum. Mephenesin was given intravenously with saline-and-glucose infusions through a fine polythene tube. Injections of 300,000 units of penicillin were given four-hourly, and 300,000 units of procaine penicillin daily. The mephenesin (given as a 1.6% solution in isotonic saline) was run in intravenously rapidly for the first 15 minutes, by which time muscle spasm was abolished, the jaw could be opened well, and relief of pain seemed complete.

The patient fell asleep without a sedative but could be readily roused. Paraldehyde, 4 ml., was given intramuscularly on this and the next night, but no other sedative or analgesic was needed. Mephenesin was continued intravenously for 42 hours, 30 g. being given in the first 24 hours, and a total of 40 g. in 42 hours. Muscle relaxation was readily attained without any observable depression of respiration. At one stage during the administration of mephenesin the patient complained of headache, and it was found that the blood pressure had fallen to 70/50 mm. Hg. This was restored to 170/110 mm. Hg, with relief of headache, by slowing down the rate of administration of mephenesin and raising the foot of the bed.

While under the influence of mephenesin a polythene tube was passed through the nose into the stomach and feeding was started with fortified milk and glucose in orange juice. After the first 42 hours mephenesin was given by the per-nasal tube. Spasm was adequately controlled by doses of 2 g. two-hourly for three days, and then by 2 g. four-hourly for one day. Retching occurred when the effect of the mephenesin was wearing off, but would cease with the next dose of the drug. After the per-nasal tube had been in position three days the patient complained of substernal pain, presumably due to oesophagitis, but this settled down without treatment. On finally withholding mephenesin, the neck muscles were somewhat hypertonic, but the patient was free of pain and could open her mouth almost as wide as normally.

When she was able to talk she recalled incidents that suggested two possible portals of entry. First, after being fitted with new dentures four months earlier, she repeatedly bit the inner surface of the left cheek; hence the indurated ulcer in the mouth on admission. Secondly, three to four weeks before the onset of symptoms, on going indoors after playing with children on a patch of sand in a corner of a paved yard, she found that the sole of her left slipper was torn and there was a little blood beneath the great toe. She could not see a wound, nor was there any sign of a wound on her admission to hospital.

COMMENT

This case illustrates the benefit obtained from mephenesin given at first intravenously and later by stomach tube. Oral administration was precluded by spasm of the jaw, and is said to entail a risk of inhalation because of its local analgesic action (Newhouse *et al.*, 1950). There was no evidence of intravascular haemolysis, probably because a solution of less than 2% was used intravenously (Pugh and Enderby, 1947; Schlesinger *et al.*, 1948). The only undesirable complication was temporary hypotension during a period of slight overdosage, presumably due to poor venous return with flaccid muscles; faintness in the erect position has been reported by Gammon and Churchill (1949).

Difficulty in diagnosis was experienced because no obvious portal of entry was evident at first, the patient presenting with pain and spasm predominantly in the left jaw. The initial unilateral distribution of pain and spasm suggests that this may have been an instance of local tetanus with the ulcer of the mouth as portal of entry. It seems more likely, however, that this was a case of generalized tetanus of only moderate severity (second degree of Cole, 1935), in which repeated trauma to the left temporo-mandibular joint caused by ill-fitting dentures may have determined the distribution of pain and spasm.

This experience emphasizes the wisdom of regarding any case of trismus as tetanus unless it can be accounted for by a definite local lesion.

My thanks are due to Dr. Russell Fraser, under whose care this patient was, for permission to publish this report.

W. HAMILTON SMITH, M.D., M.R.C.P., M.R.A.C.P.

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Reviews

BRITISH MEDICAL PRACTICE

The British Encyclopaedia of Medical Practice. Second edition. Under the general Editorship of the Rt. Hon. Lord Horder, G.C.V.O., M.D., F.R.C.P. Vol. 1: Abdominal Emergencies to Anus Disease. Vol. 2: Aphasia to Boils and Carbuncles. Vol. 3: Bone Diseases to Cor Pulmonale. Vol. 4: Cornea, Injuries and Diseases, to Ear Diseases. Vol. 5: Ecthyma to Gassing and Poison Gases. Vol. 6: Gastritis to Hypermetropia. Vol. 7: Hypnotism to Larynx Diseases. Vol. 8: Latah and Amok to Motor Neurone Disease. Vol. 9: Mouth Diseases to Pinta. Vol. 10: Pituitary Gland Diseases to Retina Diseases. Vol. 11: Rheumatic Infection, Acute, to Syphilis. Vol. 12: Talipes to Yellow Fever. (£3 5s. per volume.) London: Butterworth and Co. 1952.

With the appearance of the twelfth volume of the *British Encyclopaedia of Medical Practice* the second edition is brought to a close. It forms one of the most ambitious medical publishing ventures undertaken since the war.

The adjective "medical" in the title must be given its broadest connotation, for it includes articles on surgical, gynaecological, and specialist topics as well as those concerned with medicine in its narrow sense. It must be addressed, therefore, to the general practitioner; although its range is wide, the individual contributions are didactic and, for the most part, brief. It does not attempt to vie with the exhaustive systems of medicine of which "Allbutt and Rolleston" was the archetype. It is therefore by its appeal and value to the general practitioner that its success must be judged.

The alphabetical arrangement favoured by the editor is not immune from criticism. It may be asked whether a systematic design would not have made cross-reference easier and prevented some omissions. Some articles appear under "Heart Disease," for instance, but others, in different volumes, under "Angina and Coronary Occlusion" and "Cor Pulmonale." However, the alphabetical scheme facilitates the inclusion of such general topics as aviation medicine, contraception, and hypnosis, which would be difficult to accommodate in a systematic plan, though the reader cannot make full use of the *Encyclopaedia* until the general index is available. But this is a criticism of design and perhaps not a valid one, for the *O.E.D.* has it that the information in an encyclopaedia is "usually arranged alphabetically."

Unstinted praise can be given to the substance of the work. The breadth of its scope has been already noted; it appears to contain information, at once precise, practical, and adequate, on every subject likely to interest the general practitioner. It is not restricted to the recognition and treatment of disease, but includes contributions on such matters as medical jurisprudence, medical ethics, and medical etiquette.

Lord Horder has collected a team of authors, each of whom is able to write with authority and clarity on his particular subject. Prolixity has been controlled, ambiguity eradicated, and controversy discouraged by a firm editorial policy. It would be invidious to select articles for special mention when attempting to review the complete work; it can only be said that innumerable random samplings were constantly rewarded by concise, well-informed, and practical advice.

The editor and publisher are to be congratulated no less on the completion of this ambitious project than on the way in which it has been carried out. The typography is of an unusually high order, the illustrations are well produced, and the format is sumptuous. It presents in a handsome form a comprehensive picture of British medical practice to-day.

R. BODLEY SCOTT.

HEALTH SERVICE GUIDE

The National Health Service: A Guide for Practitioners. Edited by Max Sorsby, L.M.S.S.A. Foreword by Sir Allen Daley, M.D., F.R.C.P. (Pp. 267. 12s. 6d.) Edinburgh and London: E. and S. Livingstone. 1953.

There are people who like the Service and people who dislike it. But, apart from the last two chapters, this book is factual. It deals with what is the position now after five years, and it is written by a collection of men who have the most extensive and intimate knowledge. All of them hold responsible posts inside the administration, and have to use the intricate business organization which is explained here.

The introduction of a comprehensive health service for the nation was a task of the greatest magnitude. Very few people realize how much organization was required to provide an efficient working service and at the same time to protect the interests both of the lay public and of the medical professions concerned. While reading this book one is continually surprised at one's ignorance of quite important details, and without question it should be read from cover to cover by all doctors in the Service. It is a book for the older general practitioner or consultant, to point out the gaps in his working knowledge. It is a book to guide the young entrant, and it is particularly a book for grumblers, who may often find that their complaints are ill founded in ignorance. Ignorance of the law is no defence, and general practitioners are notorious for their dislike of learning new regulations.

Near the end of the book is a chapter by Dr. Sorsby which is full of sensible suggestions for improvements, such as, "The practitioner's responsibility in an acute case should end with notification to either the local hospital or a central agency that the patient requires admission." In a final chapter Dr. Horace Joules looks towards the future and raises controversial subjects, but no one can disagree with him when he reiterates, "The administrator exists to serve those with whom he works and not to dominate."

It is quite a short book, but it covers all the essentials. It should be read by everyone whose heart is set on making the new Health Service something of which future generations may be proud.

G. O. BARBER.

THE BILE PIGMENTS

The Bile Pigments. By Professor C. H. Gray, M.D., D.Sc., M.R.C.P., F.R.I.C. Methuen's Monographs on Biochemical Subjects. (Pp. 142. 9s. 6d.) London: Methuen. 1953.

Knowledge of the chemistry and metabolism of bilirubin and allied compounds has grown rapidly in the last few years. This monograph gives a convenient and much-needed survey of the present state. Professor Gray discusses the chemistry and properties of these compounds; the formation of bilirubin from haemoglobin; the further changes that take place in the intestine; and the nature of stercobilin and urobilin.

Recent investigations have an important bearing on two tests. The breakdown of the haemoglobin of red cells, at the end of their life span, accounts for about 70% only of the bile pigments. There are at least two other sources. Of the bilirubin excreted by the liver as little as 15% may be recoverable as stercobilin in the faeces. Nevertheless, stercobilin excretion provides a rough measure of the rate of haemoglobin breakdown (p. 48). Of the "biphasic" reaction Professor Gray writes: "The observation by van den Bergh that sera from patients with obstructive jaundice and haemolytic jaundice differ in their behaviour towards the diazo reagent provided a valuable diagnostic aid, the value of which was confused by many who attempted to correlate speed of development of colour with whether the jaundice was obstructive by nature or due to liver damage" (p. xiii). "It is clear that the type of direct van den Bergh reaction in regurgitation jaundice, whether due to extra-hepatic obstruction or to the intra-hepatic obstruction of hepatogenous jaundice, depends solely on the

concentration of bilirubin in the serum and not on the nature of the jaundice" (p. 83). May we hope that we have heard the last of the biphasic reaction?

It is generally assumed that, in the diazo reaction, bilirubin is split into two dipyrryl compounds which react with the diazo reagent. Professor Gray suggests that a catalyst in the bile may be reabsorbed in regurgitation jaundice and promote this reaction and, possibly, the excretion of bilirubin by the kidneys.

The book also contains descriptions of laboratory tests and a discussion of certain outstanding problems such as the cause of kernicterus.

J. R. MARRACK.

CONFERENCE ON POLIOMYELITIS

Poliomyelitis: Papers and Discussions presented at the Second International Poliomyelitis Conference. (Pp. 555; illustrated. £3.) Philadelphia and London: J. B. Lippincott. 1953.

This book contains a full account of the communications and subsequent discussions at the second International Poliomyelitis Conference held at Copenhagen in 1952, and it must be rare indeed for such a magnificently produced and lavishly illustrated volume to be devoted to the proceedings of an international medical conference. The papers are on all aspects of the disease and closely related subjects; they include two informative accounts of the Coxsackie viruses. Probably the most fundamental work described is that of Dr. John Enders, who gives a full account of multiplication of the poliomyelitis virus in tissue culture, a method already yielding new information about the virus. The book will be valuable for reference and is well worth the attention of those interested in any aspect of poliomyelitis who did not attend the Copenhagen conference.

J. W. ALDREN TURNER.

POLYGLOT CASE-TAKING

Polyglot Medical Questionnaire. By S. Chalmers Parry, M.A.(Cantab.), M.R.C.S., L.R.C.P., D.P.H. (Pp. 62. 18s. 6d.) London: H. K. Lewis & Co. 1953.

This book makes it possible to take a history when doctor and patient have no language in common. The text, in 12 languages, consists of 191 numbered questions, phrases, and words. The doctor finds his question in his own language, and points to the words following the same number in the patient's language. The patient then points to "Yes" or "No" in his own language, and the doctor reads the translation of this opposite the same number in his own language. If the answer is a number, this is written down or counted on the fingers. The text is divided into five sections: (1) questions on past medical history, (2) a question on family history, (3) drugs, (4) diet, and (5) general medical vocabulary. The subject matter is specially suited to the needs of ship surgeons, port health officers, aerodrome medical officers, immigration authorities, and masters of cargo vessels not carrying a doctor. The author has had many opportunities of testing the method in his work as a ship surgeon and port health officer.

The text exists in 27 languages, and the unpublished 15 translations referred to ought to be included in the next edition. Room could be found for them by omitting the first half of the book, which consists in a laboured description of the method and superfluous worked examples. All that is needed by way of introduction is one paragraph, such as the first of this review, at the head of each translation.

Not every question could be answered by "Yes," "No," or a number, and perhaps the author would add the indispensable "I don't know" as item 192. There are several omnibus questions that cannot possibly yield satisfactory answers. For example, question 24 asks if the patient has had five named diseases; each name should be preceded by a number in brackets to enable the patient to answer about each disease separately. The type is too small for easy reading, and the low, wide page (cheque-book style) is very inconvenient. These points deserve the attention of author and publishers, for the aim and method of the work are excellent. The book has all the makings of a classic that could be used throughout the world.

RAYMOND WHITEHEAD.

PARASITES OF MAN

Human Parasites and Parasitic Disease. By K. D. Chatterjee, M.D.(Cal.). (Pp. 766; 315 figures. £6 or $16.75.) Calcutta, India. Obtainable from Messrs. Das Gupta and Co. (54, College Street).

This large volume of 766 pages, which include about 50 pages of references, treats of the parasitic protozoa and helminths of man and the diseases they cause. The section on the protozoa occupies more than half the book and gives special attention to malaria, amoebiasis, and leishmaniasis. In the helminthology section the author gives chief prominence to *Wuchereria, Dracunculus,* hookworms, and taeniid cestodes. The schistosomes are less thoroughly covered in the 19 pages allotted to them, while onchocerciasis is inadequately discussed in two pages. Apart from this disproportional emphasis, which gives the impression that the author has more experience in some parasitic infections than in others, the subject-matter throughout the book is well presented, and the arrangement and headings are first-class. The book is lavishly illustrated with pictures in colour, half-tone, and black-and-white; most of them are excellent both in reproduction and in conception. In textbooks of this size minor misstatements and inconsistencies seem to be inevitable, and this one is no exception, but on the whole a high standard of accuracy is maintained. Reference is frequently made to the zoological classification of the parasites. In this respect it is surprising to note that "Helminthes," a name which has no standing in systematic zoology, is given the rank of phylum, and the Platyhelminthes and Nemathelminthes are downgraded to subphyla.

In spite of the book's shortcomings, the author, who is also the publisher, is to be congratulated on a very useful and for the most part up-to-date compilation. The writer of the foreword is well justified when he refers to its "truly beautiful format and the magnificently clear print on high-class paper which makes the letterpress a joy to read."

J. J. C. BUCKLEY.

CLINICAL PAEDIATRICS

Survey of Clinical Pediatrics. By Professor L. B. Slobody, M.D. (Pp. 471. £3 4s.) London: McGraw-Hill Book Company. 1952.

This book is a thoroughly American account in an almost synoptic form. It should prove useful to American medical students who want an easily read book on the chief facts of disorders of childhood. It is inevitable but regrettable that European literature and views should be ignored. A list of books for collateral reading and for reference is exclusively American except that one author, now an American citizen, happened to be a school-fellow of the reviewer. This national bias is unfortunate and raises the question of why the publishers should try to secure sales in England. An example of the weakness thus displayed is to be found in the section on coeliac disease; it ignores the work in Holland and England on gluten which fundamentally affects the whole question of treatment. The few remarks on breast-feeding are almost half-hearted. For students it is also surely misleading in discussing tetany of the newborn (a very rare disease anyway) to state that "the immediate treatment is to give calcium" when the urgent need is for some sedative while the calcium administration takes effect. The reviewer is undoubtedly prejudiced, because, of the long list of questions at the end of each chapter, he could rarely answer more than a fifth. The book is well printed on fine paper and beautifully produced, but it costs a lot of English money.

ALAN MONCRIEFF.

BRITISH MEDICAL JOURNAL
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THE CONTROL OF CROP PESTS

Within the last decade there has been a great development in the use of chemicals for plant protection. Many highly efficient insecticides, fungicides, and herbicides are now widely used. Some of them are exceedingly poisonous, and their toxicity prompts the question whether the benefits from their use are sufficient to offset the risk of using them. Perhaps the chief risk at present is from the insecticides. Two cases of poisoning due to a new one are reported by Dr. P. Lesley Bidstrup and her colleagues at page 1068 of this *Journal*.

After the successful introduction of the insecticides D.D.T. and B.H.C. at the beginning of the last war many new synthetic chemicals have been tested as insecticides, and a considerable number are now in commercial use. Most of these can be broadly classified into the two groups of chlorinated hydrocarbons and organo-phosphorus compounds. All of them are appreciably toxic to mammals and most of the organo-phosphorus compounds are highly toxic. The more important chlorinated hydrocarbon insecticides in current use are D.D.T. and some of its analogues, B.H.C. and its purified γ isomer "lindane," "chlordane," "toxaphene," "aldrin," and "dieldrin." The chief organo-phosphorus compounds are "parathion," "T.E.P.P.," and the systemic insecticides "schradan" and "systox."

Some of these materials are replacing other dangerous chemicals that were formerly used. The chief insecticides used before the war for plant protection were the arsenates, nicotine, and derris, and the replacement of the arsenates by D.D.T.—for example, to control codling moth—may lessen rather than increase the risk of poisoning. Again, there is probably not much difference in the risk of using T.E.P.P. instead of nicotine for the control of aphids, since both are acutely toxic and the rapid hydrolysis of T.E.P.P. compensates for the volatility of nicotine. Derris has for long been considered safe, and its replacement by B.H.C. or D.D.T. for flea beetle control and other purposes slightly increases the risk.

But often enough the new insecticides are being used to control pests for which there was previously no effective treatment that could be applied economically. An outstanding example in Britain is that of wireworms attacking cereals, potatoes, and other crops. Severe wireworm attacks often follow the ploughing up of grassland, and it may be impossible to plant cereals or potatoes unless some control measure is adopted. In the two world wars, when the acreage under cereals and potatoes had to be rapidly increased, the inability to control wireworms was a very serious matter. No chemical method of control that was economically possible was available before the introduction of B.H.C.: now control can be obtained by means of a number of newer chlorinated hydrocarbon insecticides, and this alone is perhaps a major safeguard to our food supply—not in Britain alone but all over the world, for wireworms are destructive pests in many countries.

Less important examples of the benefits of using the newer insecticides in Britain are the virtual elimination of apple blossom weevil and apple capsid from commercial apple orchards, and of the tomato moth caterpillar from commercial glasshouses. Further, there has been much more certain control of winter moth caterpillars and apple sawfly. All these insects are dangerous pests. D.D.T. has also provided a control for carrot fly, pea moth, and pea aphid which was not previously available. The organo-phosphorus systemic insecticides are proving most useful for the control of aphids on strawberry plants and brussels sprouts, and have provided the first really satisfactory control of red spider and aphis on hops.

The newer insecticides can also keep in check many other pests which are common overseas; they control or prevent locust and grasshopper attacks in various parts of the world, cotton pests in the U.S.A., Egypt, and the Anglo-Egyptian Sudan, Mediterranean fruit fly in the Middle East, and coffee berry borer in Brazil. Dr. F. C. Bishopp, of the U.S. Department of Agriculture's Bureau of Entomology and Plant Quarantine, has described[1] how crop yields in the U.S.A. have been greatly increased by the use of insecticides, most of which are the new synthetic materials. The crops mentioned include cereals, potatoes, sugar, cotton, fruit, and timber. In one instance over a million acres of small grain in Texas and Kansas became heavily infested with greenbugs, which threatened to wipe out the crop. Before the introduction of the new insecticides no control could be found for this pest, but now parathion is effective. Another example[1] where increase in crop yield could be directly attributed with some certainty to the use of the newer insecticides was that of the pests attacking the aerial parts of potatoes. In order to obtain a crop at all in some parts of the U.S.A.

[1] *Agricultural Chemicals*, July, 1951.
[2] *British Medical Journal*, 1953, **1**, 717.

potatoes must be sprayed to control Colorado beetle, flea beetles, and various species of sucking insects. Some control had been obtained with sprays containing arsenic, nicotine, and rotenone, but the introduction of D.D.T. resulted in the yield rising from 155 bushels per acre in 1946 to 211 bushels in 1949.

While there are therefore strong reasons for using the newer insecticides, they have some serious disadvantages in addition to toxicity to mammals. Though controlling one pest, they have sometimes permitted another species to increase and become a pest. For instance, the use of D.D.T. to control codling moth can result in serious outbreaks of red spider mite, because the D.D.T. destroys the beneficial insects that normally keep the mite in check. Not only are the newer insecticides highly insecticidal on immediate application, but some remain toxic both by contact and ingestion for quite a long time after application. They may therefore kill a wide range of insect species, including the beneficial predators, parasites, and pollinators. For this reason great care must be exercised in the selection and use of any new insecticide if seriously harmful effects are to be avoided. Some mistakes have already been made, and it seems inevitable that others will occur in the future. They should not be made an excuse for abandoning the search for better means of chemical control, but point to the need for further research to increase our knowledge of the interaction of the insecticide with its biological environment so that it can be used to the best advantage.

While the increase of food supplies and other essential crops obtained by means of the newer insecticides is the justification for their use in spite of their poison risk, it is essential that all concerned with their use should enforce measures to reduce those risks to a minimum. In addition to the safety regulations normally in force for the manufacture and transport of poisons, there are also the Agriculture (Poisonous Substances) Regulations, 1953. These were introduced as a result of the work of Professor S. Zuckerman's second working party, and were commented on recently in these columns.[2] A third working party under Professor Zuckerman's chairmanship is now considering the risks to the natural flora and fauna of the countryside from toxic substances used in agriculture. The risk of chronic toxicity is much more difficult to assess and to eliminate. Permissible residue limits may be set, but it is not easy to ensure that they are adhered to. This problem is particularly difficult with systemic insecticides, where the chemical is absorbed and translocated by the plant and may be continually picked up by the roots if the soil contains it. This aspect is receiving attention from all the parties interested in the application of chemicals for plant protection. In 1942 the Ministry of Agriculture and the Department of Agriculture for Scotland, in collaboration with the Association of British Insecticide Manufacturers, started a voluntary scheme for the approval of crop protection products; this has already proved to be a considerable safeguard. Finally, research is being carried out to find synthetic insecticides that are less toxic to mammals. "Malathon," one of the recently introduced organo-phosphorus series, is said to have a low toxicity, and "allethrin," a synthetic product with molecular structures based on those of the active constituents of pyrethrum flowers, is regarded as having a negligible poison risk.

EPIDEMIC HAEMORRHAGIC FEVER

In no field does travel broaden the mind more than that of nosology. Whether the travel is historical or geographical, it brings contact with disease entities which are strange and even unrecognizable within the limited experience of Western Europe in the present century. The military physician, whose activities are characterized by movement, must therefore expect the unexpected, and he was often sharply reminded of this in the last war, particularly by his encounters with scrub typhus. Korea has provided similar adventures, the two most interesting being encounters with encephalitis due to the Japanese B virus and with epidemic haemorrhagic fever. The aetiology of the first of these was known, but it presents epidemiological problems which are as great as those of poliomyelitis. The second had been previously studied by Russian and Japanese workers, though it was almost unknown to Western literature. The only positive statement which can be made about its aetiology is that the cause and the mode of infection are not known. Analogy and some observation have in turn suggested a leptospira, a virus, and a rickettsia. The first can probably be excluded, but the evidence to incriminate either of the others is remarkably weak.

The disease, 40 cases of which are reported on by Captain R. Andrew in our opening pages, presents a clear-cut epidemiological picture. It is known to occur in Manchuria and now in a limited area of Korea north of Seoul. It appears as an epidemic

1 McNinch, J. H., *Ann. intern. Med.*, 1953, **38**, 53.
2 Ganong, W. F., *et al.*, ibid., 1953, **38**, 61.
3 Counts, E. F., and Seltser, R., ibid., 1953, **38**, 67.
4 Kessler, W. H., ibid., 1953, **38**, 73.
5 Hullinghorst, R. L., and Steer, A., ibid., 1953, **38**, 77.
6 Swift, W. E., ibid., 1953, **38**, 102.
7 Leedham, C. L., ibid., 1953, **38**, 106.
8 Barbero, G. J., *et al.*, *Arch. intern. Med.*, 1953, **91**, 177.
9 Katz, S., *et. al.*, *J. Amer. med. Ass.*, 1953, **150**, 1363.
10 Powell, G. H., ibid., 1953, **151**, 1261.
11 Thucydides. *The History of the Peloponnesian War*. Trans. R. Crawley. London: J. M. Dent. 1936.

showing well-marked separation into two peaks, the first in mid-summer, the second in autumn, each separated by about a month. The incubation period lies somewhere between seven and thirty days. Because contagion from known cases does not occur, an insect vector is believed to spread the disease, and there is slight support for the incrimination of a mite which normally lives on rodents. The epidemic area in Korea is small, and, being mainly occupied by U.S. troops, the brunt of the disease has fallen on them, the Commonwealth Division fortunately having a limited experience of it.

Initially the patient shows toxaemia with severe incidents of shock during which death is not uncommon. Pathological examination discloses numerous foci of coagulative necrosis in the adrenals, pituitary, kidneys, and other organs, which may be the centres of concentration of the toxin involved. There is marked fragility of the capillary system; in its full extent it appears after the height of the toxaemia—about the tenth day—with consequent haemorrhage widely distributed but particularly common in the kidneys, nasopharynx, and, as necropsy shows, in the right auricle of the heart. Clinically, the initial toxaemia and early severe shock are accompanied by some haemorrhage, but this is followed by a more haemorrhagic stage. Death is most common in the early stages, when it is due to shock, or it may come later and is then usually due to renal insufficiency. Convalescence is slow but apparently complete. No specific therapy seems to be effective; the greatest benefit comes from nursing and the avoidance of trauma from the moment the disease is first recognized, while parenteral fluids may be dangerous. The account of the Commonwealth Division's experience described by Captain Andrew reinforces the greater experience of U.S. forces, much of which is brought together in a recent symposium.[1 2 3 4 5 6 7] Clinical and laboratory accounts have also been given by Barbero *et al.*,[8] Katz *et al.*,[9] and Powell.[10] To put the matter into proper perspective the reader could well turn to Thucydides'[11] account of the plague of Athens, and, realizing how similar the two cases are, understand our ignorance of the distribution of disease in time and space.

TREATMENT OF HABITUAL ABORTION

A great variety of remedies have been tried in the treatment of habitual abortion, remedies with nothing in common between them except a high rate of success. Such good results may therefore be due not to the particular treatment but to the special care and attention bestowed on these women. This possibility is emphasized by a report by Bevis[1] on 32 patients with three or more successive spontaneous abortions, 81% of whom, after extensive investigations but no specific treatment, were delivered of living babies. Thus it becomes desirable to try to determine by a controlled series of cases the relative therapeutic importance of the psychological factor. And when Bishop and his colleagues[2 3] recently reported excellent results with progesterone implants they were to this end challenged to treat alternate cases with implants of an inert compound. For reasons given[4] the challenge was declined, but on page 1073 of this issue of the *Journal* Dr. G. I. M. Swyer and Miss Doreen Daley describe a clinical experiment along similar lines. They present a series of 107 women with two or more consecutive spontaneous abortions before the twentieth week, in whom no general or local lesion of obvious significance was found. Progesterone was implanted in 55 of the women, while the remaining 52 received no specific therapy. The success rate in terms of living babies was 81.8% in the treated cases and 75% in the untreated, an insignificant difference. Moreover, studies of urinary pregnanediol excretion in both groups suggested that a large proportion of the abortions occurred in spite of apparently adequate progesterone metabolism, and there was no increase in pregnanediol excretion in the women in whom progesterone had been implanted. They conclude that progesterone deficiency is not an important cause of habitual abortion and that progesterone implants are not the solution to the therapeutic problem.

But in several respects this series of cases was not ideal for the purpose of this clinical experiment. First, the spontaneous cure rate after two consecutive abortions is so high that abortion should be termed habitual only after three or more consecutive miscarriages, and only 44 of the 107 women were thus qualified. In these the success rate was 79.2% in the 24 treated patients against 55% in the 20 untreated, a difference greater than in the whole series but still not statistically significant. It would also have been preferable to have excluded all women who had borne live babies before the abortion sequence. Secondly, the controls would also ideally have had implants inserted although of inert substances. And, thirdly, there is no proof, although it is tempting to infer, that the urinary excretion of pregnanediol is an accurate index of the progesterone metabolism. This report by Swyer and Daley, therefore, while welcome because it provides further evidence on a difficult problem, does not enable a final judgment to be made.

Another possibility which would explain the high rate of success attending different forms of treatment in habitual abortion is that the rate of spontaneous cure is higher than that given in the widely quoted calculations of Malpas[5] and Eastman.[6] This is a possibility which has occurred to many obstetricians, and Swyer and Daley present several criticisms of these calculations. Even so these figures were not advanced to be

1 *Lancet*, 1951, **2**, 207.
2 *British Medical Journal*, 1950, **2**, 130.
3 Ibid., 1952, **1**, 244.
4 Ibid., 1952, **1**, 604.
5 *J. Obstet. Gynaec. Brit. Emp.*, 1938, **45**, 932.
6 *Williams' Obstetrics*. 10th ed. New York: Appleton-Century-Crofts. 1950. p. 490.

used as a yardstick against which to measure the success obtained in treating a condition of varying aetiology by a single method. Further, Swyer and Daley compare the success rate in their untreated cases in a series from which women with obvious causes for their disability have been excluded with the rate of spontaneous cure calculated for all cases of repeated abortion.

From the viewpoint of the general practitioner the position is not yet clear-cut, and the relative frequency and importance of the various causes of habitual abortion have not yet been determined. When consulted between pregnancies by a woman with such a history, his best course would be to carry out general and local investigations to try to detect the cause. If pregnancy is already established, he may in addition administer any or none of the popular remedies, but he might well concentrate chiefly on inspiring the patient with confidence in the outcome of the pregnancy.

TROPICAL DISEASES IN BRITAIN

The presence of our forces in the Far East, particularly those fighting in Korea and Malaya, must renew the interest of the practitioner in this country in diseases of the Tropics. In particular he should be aware of those which may persist in Europeans after their return to Britain. Attacks of malaria, especially of benign tertian (*P. vivax*) malaria, may occur in men home from these areas. The measures now taken by the Army au horities include the daily administration of proguanil ("paludrine") for the prevention of illness due to malaria, replacing the mepacrine so well known during the 1939–45 war. This prophylaxis has proved extremely efficient in suppressing the manifestations of malaria while the drug is being taken regularly. However, unhappily no drug has so far been found which can safely be given to prevent a B.T. malaria infection. It follows that when the suppressive drug is stopped on leaving the Far East a suppressed infection may come into the open as an actual attack of B.T. malaria in a period of anything from a few days to nine or ten months after a man's return home. These are the cases that the doctor in this country may meet, and the difficulties in diagnosis are not lessened by the fact that the patient has not suffered from malaria while overseas, and that he has remained well for a considerable period after his return home and re-entry into civil life.

Every febrile condition occurring in repatriates from the Tropics within 12 months of their return should be suspect as an attack of malaria, regardless of a previous history of freedom from this disease. A first and elementary step in its investigation should always be an examination of blood films for malaria parasites. Any treatment in advance of this blood examination is most undesirable, as it may vitiate the diagnosis. The inferential, or "therapeutic," diagnosis of malaria is unwarrantable when a simple blood examination will put the matter beyond doubt. If the prompt examination of blood films is impossible, at least the films themselves can usually be made before treatment is begun, and subsequently studied to make the diagnosis. Perfectly satisfactory thick blood films have been made in exceptional circumstances on pieces of window glass. Once diagnosed an attack of benign tertian malaria becomes a matter of minor significance. The infection can rapidly be controlled, and furthermore it can be completely eradicated within a week or two in a high proportion of cases; in any event it spontaneously disappears within, at most, two years of its acquisition. Under such conditions the disability resulting from it is transitory and trivial.

Among other possible sequels of service in the East are intestinal infections with protozoa and with worms. These occur wherever sanitation is defective. Worm infections of the bowel in otherwise healthy Europeans are of little significance. While aesthetically unpleasant, they rarely cause ill-health. True hookworm disease occurs only in debilitated populations suffering from heavy infestations superimposed on malnutrition and the avitaminoses; it is not seen in the well-nourished. The eradication of roundworms and of hookworms, if these are present, is quite a simple matter.

Of the protozoal infections of the bowel amoebic dysentery is by far the most important. Persistently recurring diarrhoea, sometimes with the passage of blood and mucus (dysentery), should raise suspicion of *Entamoeba histolytica*. Its detection rests on examination of the stools by an experienced pathologist. As in malaria, and indeed any other parasitic infection, the diagnosis is established only on recovery of the parasite, and "therapeutic" diagnosis is to be deprecated. Emetine, though very remarkable in treatment, should find no place in diagnosis.

A well-known and not very uncommon complication of old-standing amoebic dysentery is amoebic liver abscess. It may appear some years after repatriation to the temperate climates, and it must be considered as a possibility whenever an increasing lesion of the liver with acute ill-health makes its appearance after sojourn abroad. Occasionally an amoebic liver abscess develops in a person who gives no clear history of previous diarrhoea or dysentery; early diagnosis then is one of the most difficult in the field of tropical medicine.

If efficiently diagnosed and treated the after-effects of amoebic dysentery or of a complicating amoebic liver abscess are as a rule negligible. It is therefore a prime duty of the physician in this country to be alert for these readily controllable and eradicable malarial and dysenteric infections in ex-Service men.

FIBROSITIS AND ADRENALINE

Fibrositis is a useful diagnosis. It requires the very briefest history; a single word may be sufficient—pain. For physical examination a single prod eliciting tenderness may be enough. The difficulties in the way of studying such a condition are immense, since its major component is a subjective one, and, as Kellgren[1] said, there is an "appalling confusion which has arisen through careless and inaccurate translation of sensory experience into words." So far as fibrositis is concerned,

confusion began when Gowers,[2] writing about lumbago in 1904, coined the term "fibrositis," a word with specific pathological implications. And when Stockman[3] later apparently demonstrated inflammatory changes an erroneous idea became firmly established. There is now a great deal of evidence that fibrositis is simply a clinical syndrome with many different causes, not all of them inflammatory in nature. The pioneer studies of Sir Thomas Lewis[4] and of Kellgren have done much to clarify our understanding of the mechanism of deep referred pain, and it is now recognized that many joint and ligamentous disturbances are responsible for what was hitherto considered to be fibrositic pain. The wide recognition of the importance of the intervertebral disk and its associated structures as a cause of pain reflects our expanded knowledge.

The high morbidity of this condition has recently been emphasized by the Leigh Survey,[5] a field survey into the incidence of rheumatic complaints in an urban population. The various transient painful syndromes of this type had to be categorized as "undetermined" in view of the absence of adequate diagnostic criteria. It was found that about 5% of the adult population was suffering from this group of conditions at the time of the survey. Any claims to have discovered a new method of treatment of such a common and important group of conditions must be reviewed against this background. Not only is fibrositis ill-defined, but the symptoms are subjective and usually transient, while some 10% of the population suffer from an attack during a five-year period. The original claims made for adrenaline cream by Moss[6] therefore fell on fertile ground. He reported on his results in 106 cases of lumbago, fibrositis, migraine, and peri-arthritis, and made the claim that, except for those cases with early osteoarthritis, practically all his patients were symptom-free in an average time of 9.5 days. Later Howell[7] supported these findings and added some evidence that adrenaline cream gave greater relief than simple cream. On the strength of this work, and supported by an efficient advertising campaign, adrenaline cream came into common use.

An attempt to verify the efficacy of adrenaline cream was carried out by the Empire Rheumatism Council[8] in 1951. It failed to show any significant difference between adrenaline cream and a blank cream. Even so, its use continued. In the present issue of the *Journal* Dr. J. S. Lawrence and Mr. R. J. Sladden describe a further study of what has almost become a household remedy. Their clinical material included cases of arthritis with referred deep pain as well as those from the undetermined group. They found that the palliative effect of adrenaline cream in the relief of pain was no more than that produced by simple massage alone. They also found that both dry massage and adrenaline cream were better than massage with an inert lubricant. But their most interesting conclusion is that the rate of recovery is delayed by the use of adrenaline cream.

1 *Lancet*, 1949, **1**, 943.
2 *Brit. med. J.*, 1904, **1**, 117.
3 *Rheumatism and Arthritis*, p. 41. Edinburgh: Green and Co. 1920.
4 *Pain*. London: Macmillan, 1942.
5 Kellgren, J. H., *et al.*, *Ann. rheum. Dis.*, 1953, **12**, 5.
6 *Med. Wld (Lond)*, 1949, **70**, 244.
7 *Lancet*, 1950, **2**, 395.
8 Bywaters, E. G. L., *Ann. rheum. Dis.*, 1951, **10**, 359.

A POISONING ACCIDENT

Although thousands of serious injuries from motor-cars may pass almost unnoticed, the occasional case of poisoning in industry will always arouse the interest of the profession. We publish at page 1068 an account of an incident which directly involved three people handling a new material being developed for use as an insecticide. Prevention is the principle behind the practice of industrial medicine, so that it is important to see what can be learnt from an incident of this kind.

The substance responsible for the accident—"mipafox"—belongs to a large and diverse family of organo-phosphorus compounds sharing the property of inhibiting cholinesterase though varying considerably in their toxicity to animals. Some of the problems associated with the biological properties of these compounds were briefly referred to recently.[1] By laboratory tests earlier considered adequate for evaluating the toxicity of these compounds, mipafox appeared to be considerably less toxic than either "parathion" or "T.E.P.P.," both of which have been made in large quantities in comparative safety. Mipafox is a solid and so should be easy to handle safely, and it is free from any vapour hazard. It is therefore somewhat surprising that any accidental poisoning ever took place, especially as the victim most seriously affected had been handling these compounds for almost two years. But it is reported that she had experienced symptoms of poisoning on no fewer than three previous occasions during the work. This suggests that we are concerned here with a personal factor at least as important as the chemical factor. Every large laboratory includes among its staff the worker who despite a general competence often has spills and breakages. Much has been written about accident-proneness, but usually in relation to the handling of machinery. The disability is not confined to any one class of society or grade of worker. Chemists in research laboratories developing new and potentially poisonous materials are exposed to certain unknown risks in the course of early work on a new compound. Those responsible for their welfare should take care to remove workers whose liability to accidents renders their work more than usually hazardous.

A notable feature of the report is that the animal experiments had failed to reveal one of the special toxic properties of mipafox—namely, its propensity to cause paralysis. These same tests would have shown that tri-*ortho*-cresyl phosphate—T.O.C.P., or ginger jake—was completely harmless and did not even carry the risk of acute poisoning. It is a pity that those who apparently suspected that the new organo-phosphorus compounds might behave like T.O.C.P. did not feel this strongly enough to lead them to try the compounds out against the fowl, which has long been known to be the most susceptible species, apart from man, to the action of T.O.C.P. Even so, unless these workers had used D.F.P. their results would have been negative even in the bird, for work since this accident occurred has shown that only very few of the organo-phosphorus compounds developed or used to-day can produce these lesions. It is not

1 *British Medical Journal*, 1953, **1**, 983.

yet possible to suggest the chemical or biochemical properties that a compound must possess before it is capable of causing paralysis in fowls. It is easy to be wise after the event, but wiser to try to learn from it. Mipafox was originally proposed for general use as an insecticide because it was felt that its apparently low acute toxicity would make it acceptable for general use and distribution among gardeners and farmers. This unfortunate accident may well have prevented many more had this policy of general distribution of mipafox been carried out.

The growing and harvesting of crops was the earliest of civilized man's activities, and in many respects agriculture has remained technologically simple. The introduction of poisonous chemicals to reduce pests—a subject discussed in a leading article above—demands more than the techniques and experience needed to spread dung or apply lime. The successful use of such materials must depend upon their skilled application, and it is unreasonable to suppose that the average suburban gardener or farm labourer is also a plant pathologist and entomologist. Without very careful guidance he will probably fail to make effective use of special chemicals because of the same lack of knowledge and experience that may result in his poisoning himself by improper handling of them. Agriculture will not suffer if the careless use of potentially dangerous materials is restricted so far as possible. On a large scale special measures have to be taken to use toxic substances carefully. They have no place in the hands of the untrained user.

GARGOYLISM

The children to whom Ellis, Sheldon, and Capon[1] gave the name of gargoyles have, when the condition is fully developed, such a constant and bizarre association of abnormal characters that gargoylism can certainly be defined as a disease entity, even though its essential cause remains unknown. Little has been added to the clinical description of the disease since this account. The signs include mental defect, heavy features with excessive eyebrows and a depressed bridge of the nose, enlarged and often abnormally shaped head, splenic and hepatic enlargement, cloudy corneae, dwarfism, and osteochondrodystrophy. But it is now known that milder variants of the condition may occur.

The most convincing cases of these *formes frustes* are to be seen in those children with a brother or sister showing the disease in more florid form. A good example has been reported from Capetown by Jackson.[2] In this family one girl was a typical gargoyle, a brother had well-marked skeletal changes but had a normal facies and above-average intelligence, while another sister had an intermediate grade of the condition. Gargoylism in some of these milder forms has been confused with Morquio's disease, where there is a superficially similar skeletal disturbance and occasionally mental defect.[3] But Fairbank[4] has emphasized that the radiological appearances are distinctive. In gargoylism affected vertebrae in the lateral view are rounded and biconvex, with the lower part projecting as a beak, but in Morquio's disease they are flattened and often biconcave, with a central tongue-like projection.

Histologically gargoylism appears to be a storage disease. The affected organs show swollen cells with pale vacuolated or granulated cytoplasm, but the nature of the substance stored has not been settled. It is probably not a lipid. These cells, except perhaps in the brain, contain little material with the usual staining reactions of lipids. In one case[5] quantitative differential lipid analyses of liver and spleen showed values within the normal range.

Family studies of gargoylism are incomplete. No one has yet collected a large number of well-investigated family trees based on an unselected series of index cases. But already it is clear that there are forms of the disease with different genetic determinations. In 1942 Halperin and Curtis,[6] putting together the published reports, suggested that an autosomal recessive gene was responsible. This would account for the family distribution in most of the published pedigrees, and the unexpectedly few consanguineous marriages described might well be due to bad reporting. But in 1945 Njå[7] reported a Norwegian family strongly suggesting sex-linked recessive inheritance. He noted that in the affected individuals the corneae were clear. Millman and Whittick[8] have recently published an even clearer instance of sex-linked recessive inheritance, with affected males in three generations of an English family. Here again the corneae were clear. Probably this sex-linked variety will prove less common, but there is no doubt that there are at least two types of gargoylism, genetically and probably clinically distinct, and it will be interesting to see if the substance stored proves to be the same in each variety.

1 *Quart J. Med.*, 1936, **5**, 119.
2 *Arch. Dis. Childh.*, 1951, **26**, 549.
3 Whiteside, J. D., and Cholmeley, J. A., ibid., 1952, **27**, 487.
4 *An Atlas of General Affections of the Skeleton*, p. 136. Edinburgh: Livingstone. 1951.
5 Henderson, J. L., *et al.*, *Arch. Dis. Childh.*, 1952, **27**, 230.
6 *Amer. J. ment. Defic.*, 1942, **46**, 298.
7 *Acta Paediat.* (*Uppsala*), 1946, **33**, 267.
8 *J. Neurol. Neurosurg. Psychiat.*, 1952, **15**, 253.

THE SIR CHARLES HASTINGS LECTURE

An appreciative lay audience filled the Great Hall at B.M.A. House on May 6 when Professor F. A. E. Crew gave the second Sir Charles Hastings Lecture to be delivered since the war. Mr. Walter Elliot was in the chair. The subject of Professor Crew's paper was "Medicine and Social Policy," a topic which has become increasingly important as the State has accepted more and more responsibility for the welfare of the people. Professor Crew dwelt particularly on some of the weak places in our social structure, and emphasized the special needs of the aged, a subject also touched on by Mr. Walter Elliot in moving a vote of thanks to the lecturer. Professor Crew's paper will be published in a forthcoming issue of the *Journal*.

REFRESHER COURSE FOR GENERAL PRACTITIONERS

CARCINOMA OF THE BREAST

BY

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It might be thought that the busy practitioner need not concern himself with so academic a matter as the cause of breast cancer, and, indeed, this is largely true, but there are certain aspects of this problem with which he should be familiar, as they must influence the answers to everyday practical questions with which he has to deal.

It will be possible here to make only the briefest reference to work that has been done in this field, and then only when this work has a direct bearing on the problems facing the family doctor. Much of the work concerns experimental animals such as the mouse, and the application of lessons learnt in the experimental laboratory to human pathology is an exercise fraught with the possibility of error. Nevertheless, where precise mechanisms are demonstrable in operation in the lower orders of mammalia the possibility that similar mechanisms operate in the human must always be borne in mind.

Without it being possible in this article to recount the evidence in favour of the following concepts, it may be stated that three factors seem to be involved in the genesis of breast cancer in the mouse: a factor conveyed in the maternal milk, demonstrated by Bittner in 1937, without which cancer of the breast can hardly be made to appear; an endocrine factor, which is probably an oestrogen; and a genetic factor.

The Milk Factor

Nobody knows whether there is a milk factor concerned with the genesis of breast cancer in the human, but the possibility is being investigated vigorously from many aspects. Studies with the electron microscope have revealed particles in human breast milk apparently identical with the particles demonstrable in the milk of susceptible mice. Whether these particles are indeed identical, or, if they are, whether they are concerned in the human with the genesis of breast cancer, or, again even if they are, whether they are not equally transmissible through the placental circulation or by other means, are problems which only future investigation may reveal. The practical issue is that it is impossible to keep Bitner's work a secret, and even the lay public are beginning to hear rumours about it, so that it is not unknown for a woman with a family history of breast cancer to ask whether it would be better for her not to suckle her baby girl in case by so doing she implanted the germs of cancer. The answer to such a query should be unequivocally that she should suckle her baby. The benefits of this practice to both mother and child are so well known that they require no recapitulation here; but, even from the point of view of cancer of the breast, we *know* that suckling protects the mother in a certain measure from this disease, and to set against this we have as yet no substantial evidence whatever that suckling can transmit a responsible factor to the offspring in the human. Even if such evidence were forthcoming it would be illogical, by refraining from suckling, to subject the baby to an increased chance of succumbing to an infantile virus infection in order to protect her from some hypothetical risk half a century later.

Hormones

The influence of oestrogens in the causation of breast cancer in the mouse is indisputable, but the effect of these substances on human breast cancer is so bizarre, contradictory, and altogether unaccountable that again we must proceed with the greatest caution in tendering advice to patients.

The facts are that excessive doses of oestrogens do seem in a few cases to be responsible for the appearance of breast cancer. For instance, the appearance of bilateral cancer of the breast in a male subject being treated with oestrogens for carcinoma of the prostate is a striking instance of this effect. To claim that these cancers are really secondaries from the prostate is possible though unlikely, in that cancer of the prostate does not naturally behave in this way. To set against this we have the undoubted beneficial effect of equally large doses of oestrogens on certain cases of established cancer of the breast. Was ever a position more confusing? Unfortunately, however confusing the evidence, our advice to a patient must be categorical. Again we must weight the scales in favour of certainties against hypothetical uncertainties, and, as we know that oestrogens in moderate doses are of the greatest benefit to patients in some endocrine disorders, particularly about the menopause, these substances should be prescribed. Because of our uncertainties, however, it might be prudent to withhold these substances, if possible, in patients with an unusually strong family history of breast cancer or where there has been evidence of pathological behaviour on the part of the breast, as, for instance, a blood-stained discharge from the nipple. We do not know whether the prescription of oestrogens in such cases might be harmful, but we do know that if cancer of the breast did appear subsequently this event might be attributed to the oestrogens, which would put the doctor in an unenviable position from which he might find it difficult to escape.

Diagnosis

There is no positive evidence that there is any such thing as a precancerous state in the breast. It has been claimed that lumpy breasts (fibroadenosis) are more prone to cancer than others, but this tendency, if it exists at all, is very slight and no prophylactic measure other than observation is called for in the vast majority of patients found to have this complaint. It is an entirely different matter when the patient has *a lump* in the breast. In this case the lump must be removed, because, although the most intelligent guess may be made as to its nature—having regard to its shape, consistence, and other qualities, together with the age of the patient in whom it occurs—unless it is unequivocally a cancer (because it has spread outside the breast), an exact diagnosis can never be made until it has been seen, handled, cut, scrutinized, and sent for histological assay.

It is not a bad rule to make in practice that "no lady has a lump in her breast"; all solitary lumps are removed whatever their alleged nature. A few experienced surgeons would make an exception to this rule in the case of fluctuant lumps which are undoubtedly nothing more than cysts, as proved [*sic*] by the fact that all physical signs disappear when the cyst has been aspirated. To make an exception in this instance is, however, apart perhaps for

the most experienced, a dangerous practice. The number of times when *all the physical signs disappear as a result of aspiration* are so few in the practice of most surgeons that this rarity may for the time being be ignored. If we accept this rule, the only difficulty is to decide in some cases when the clinical presentation may be categorized as a "lumpiness confined to one region of the breast" which may be left alone, or stigmatized as a "lump" which must be removed. In cases of doubt it is better to remove the indurated area and make sure of its nature. The price of this precaution is a week's disturbance of the patient's routine; the result is certainty, and nothing less than certainty should be entertained.

It will unfortunately not be necessary to refresh the practitioner's knowledge of the general qualities of a lesion so common as a cancerous lump in the breast, except perhaps to recall that this disease occurs at any age after puberty, although it is rare under the age of 30 and unusual under the age of 40; furthermore, its consistence varies widely, and, whilst it is generally hard, it may be so soft as to feel fluctuant. However, if we adopt the rule stated above, that "no lady has a lump in her breast," these considerations are somewhat academic. Nevertheless, for the sake of his own interest, and in order to prepare the patient for what may have to be done, the practitioner must make the most careful examination of both the breasts and the fields of lymph drainage and so arrive at a putative diagnosis in a doubtful case. In this way he will be able to tell the patient, on the one hand, that she has a lump which might be serious but which in his opinion will probably turn out to be innocent, and so in some measure allay her fears; or, on the other hand, that she has a lump which he is afraid may lead to the necessity for removal of the breast, but that before this extreme measure is decided upon it will be established that such a procedure is essential by excising the lump itself and examining it, if necessary, with the aid of a microscope.

Treatment

The treatment of cancer of the breast is at all stages the responsibility of the specialist, but this treatment must be undertaken in conjunction with the family doctor, who will act in his traditional role as interpreter, counsellor, and champion of the patient. It is important, therefore, that he should be fully aware of the place and significance of the treatment adopted so that he can commend its prescription with confidence, interpret it with understanding, and steer his patient through it with wisdom.

Quite recently the whole edifice of therapy in carcinoma of the breast has been rocked by those who, juggling with figures, have suggested that no method of therapy prolongs life in cancer of the breast. What in fact these people have done is to challenge orthodox therapists to prove that by their interference they have prolonged the life of their patients by as much as a day. The figures, so they say, show no such thing. Fortunately for common sense, more astute jugglers have revealed flaws in the statistical arguments of the former group and claim that the evidence available indicates, with a degree of likelihood which no reasonable man could ignore, that life is indeed prolonged by treatment. In addition to this, the quality of that life is enhanced immeasurably by treatment, so that the patient is saved from the sickening embarrassment of a fungating mass on the chest wall or an uncomfortable and frightening lump in the axilla.

Treatment, then, should be prescribed—but what? Three forms are available: surgery, radiotherapy, and hormone treatment, or a combination of these three. Many schemes of treatment are in vogue, and to judge between them is very difficult. After all, if it can be seriously contended that a difference statistically between treatment and no treatment scarcely exists, although this view has been exposed as false, it may well be appreciated that a statistical comparison between different methods of treatment varying but little in their efficacy is a complicated problem.

The reason for this difficulty is that there is probably a large group of cases of cancer of the breast inherently so relatively slow to metastasize that whatever reasonable method of treatment is adopted, or even if treatment is withheld, the patients will survive for 10 years or more; there is another large group so inherently malignant that whatever treatment is adopted the patients will succumb within three years. It is in the intermediate group, and perhaps only in this group, that treatment affects the survival rate, and different schemes of treatment influence this to varying extents.

The Early Case

As between surgery and radiotherapy it has been said that surgery is the best method of eradicating cancer, but that ill-advised surgery will do harm; whereas radiotherapy will nearly always restrain a growth if it does not exorcise it, and is never likely to stir it up. The treatment of breast cancer may be likened to the taking of photographs. The amateur will probably get the best overall results with a box-camera where refinement of judgment and delicacy of technique are unnecessary, but for the very best results a complicated apparatus is essential, together with a trained understanding of its use. To take an example, there is a large region of the British Isles where the "box-camera" method of treatment of early cancer of the breast has been adopted as an experiment with an unexpected degree of success. This method consists in the removal of the breast by surgery together with *x*-ray therapy applied to the axilla: this plan is pursued regardless of the details of clinical presentation. We cannot afford to ignore this bold experiment, which has thrown into vivid relief the fact that some of the very best results are obtained with the radical operation, but so are the most tragic when this method is used inadvisedly. When the delicate and careful dissection of the axilla, which is the essential feature of the radical operation, is employed with skill and discrimination it is the best way of eradicating a growth which has reached these fields but has extended no further. When it is employed in cases in which the growth has passed beyond these boundaries, then this performance may well do harm and serve only to disseminate the growth into the blood stream and accelerate the death of the patient.

In the early stages of cancer of the breast each case must be carefully considered from the points of view of both the primary and the likely fields of lymphatic extension. The fact that the most important method of spread to the glandular fields is by embolism, or, if by permeation, that the intervening strands become obliterated by fibrosis, implies that there are generally no cancerous trails leading from the primary to the secondary; therefore each can be regarded as an isolated problem. If surgery can be presumed to eradicate either the primary or a possible secondary field or both, without encroaching within the precincts of cancerous extension, then surgery is indicated. If, because of widespread extension, it is unlikely that surgery will be able to do this, then in that particular part—primary, secondary, or both—surgery were better eschewed and reliance placed on radiotherapy alone. By applying this principle the planning of treatment in a case of cancer of the breast is a problem of some nicety, and the days are gone when the wholesale prescription of radical mastectomy to Stage I cases with the addition of *x*-ray therapy to Stage II cases can be considered the best methods of treatment available. The position is further complicated by the realization that the lymph nodes along the internal mammary chain are not infrequently the first lymph nodes to become involved, especially with growths in the inner half of the breast, so that in these growths the most careful consideration must be given to the method of treatment. In all these early cases a properly balanced plan comprising surgery alone, radiotherapy alone, or a combination of these two must be enjoined.

An exception to the rule that surgery should be withheld unless it can remove the whole cancerous field may be made

in those advanced cases in which it contributes to the patient's welfare and can make little difference to the ultimate outcome if an offensive lesion is excised as a palliative measure.

In dealing with cancers in the aged, even the atrophic scirrhus of the aged, exactly the same principles apply. If the nature and extent of the growth dictate a certain line of treatment, including radical mastectomy, then the age of the patient should be no bar. Radical mastectomy is well borne by the very old, the results in these cases are excellent, and the alternative of leaving a gradually extending cancer while the patient passes in otherwise perfect health through the eighties is to subject her to anxieties, inconveniences, subterfuges of concealment, and eventually painful extensions of her disorder which are quite unnecessary.

The Late Case

So much for the early case. When the growth has spread, generally by the blood stream, to distant foci, radiotherapy applied to these foci is the best measure to adopt. If, however, these foci are multiple and widespread the use of radiotherapy is impracticable and hormone therapy is indicated. Distant metastases often occur in the skeleton, particularly in the bodies of the thoracic vertebrae, in the rest of the spine, in the upper ends of the femora and humeri, in the skull, and to a less extent elsewhere. As these deposits, in contradistinction to those caused by a cancer of the prostate, are nearly always osteolytic, pathological fracture is a common complication. These fractures should be treated as if they were traumatic fractures without a pathological basis, except that open operation with internal splintage would not be used, and, in addition, the part should be subjected to *x*-ray and hormone therapy. In this way in a surprising number of cases the fracture will heal in time for the patient to enjoy the use of, for instance, a limb before she is overwhelmed by a widespread dissemination of the disease.

When a case is beyond possibility of help by means of surgery or radiotherapy because of the widespread nature of the manifestations, and in all cases before the patient is allowed to die from the effects of this disease, hormone therapy should be tried. Judiciously applied this can practically never do harm (if indeed harm could be done to the type of patient under consideration) and in a few cases the effects are little short of miraculous, while in about half the cases the rate of dissemination of the growth is stayed.

Androgens and oestrogens are employed for this purpose. The way in which these substances work is unknown and their prescription is therefore empirical. Androgens, given as intramuscular injections of testosterone propionate in doses of 100 mg. three times a week or as methyltestosterone by mouth in doses of 50 mg. daily, are indicated in pre-menopausal women, particularly in those with skeletal deposits. Oestrogens, prescribed as diethylstilboestrol in doses of 50 mg. daily, are indicated in patients well past the menopause with soft-tissue lesions, particularly with pulmonary and pleural deposits. With both these substances unpleasant side-effects may occur. Androgens may induce masculinization and oestrogens may give rise to oedema of the subcutaneous tissue in the region of the pelvis and of the extremities, uterine haemorrhage, or nausea and vomiting. Interestingly enough these side-effects are little more noticeable with the comparatively large doses recommended in these cases than they are with the more modest quantities prescribed for other purposes.

The appropriate endocrine is prescribed indefinitely and the beneficial effect (see Figs. 1 and 2), if there be such, lasts in the case of androgens for about six to eighteen months and in the case of oestrogens for about eighteen months to two years as a rule, although in certain cases under oestrogen therapy the effect may be prolonged indefinitely. If a response has not been noted within eight weeks of beginning treatment it is not worth while persisting with it.

Complications of Treatment

Serous Effusion.—After radical mastectomy there is a tendency for serum to collect under the flaps and to pocket, and this is particularly the case in the potential dead space left by the dissection of the axilla. These collections are harmful in that they may become infected and form an abscess, or at best they heal with a great deal of fibrosis. This fibrosis will tether the flaps to the chest wall and lead to uncomfortable restriction of movement, or it may be responsible for strangulation of the few remaining lymphatics in the axilla and predispose the patient to oedema of the arm. The greatest care therefore should be taken to prevent serum collecting in this way. A "snowball" made of cotton-wool is bandaged firmly into the axillary space to obliterate this so far as is possible. The drainage tube is connected to a suction pump for 72 hours, after which time it may be disconnected and gradually withdrawn by about half an inch (1.5 cm.) a day until it falls out. Lastly, although movement of the fingers, wrist-joint, and elbow-joint is encouraged from the first, the shoulder-joint should be held still, immobilized by the firm bandage, for a week. In this way the flaps will not sheer over the chest wall and generate effusions. Should an effusion occur it should be aspirated and a firm bandage applied.

Oedema of the Arm.—Slight swelling of the arm is very common after radical mastectomy, but it is rare for this to be severe enough for the patient to complain. The pathology of this oedema is not understood. It is probably more common, as mentioned above, where a serous effusion is allowed to collect in an unobliterated dead space in the axilla, and recently it has been suggested that it is a lymphatic oedema which follows a venous oedema due to transitory obstruction of the axillary vein by a mural thrombus. Neither of these theories takes into account the fact that it is more apt to occur in fat people, and it is possible that lymphatic obstruction following fat necrosis in the axilla is a contributory factor. Certainly *x*-ray therapy enhances the likelihood of this complication. The measures outlined above to prevent serous effusion should be practised assiduously. Once the condition has been

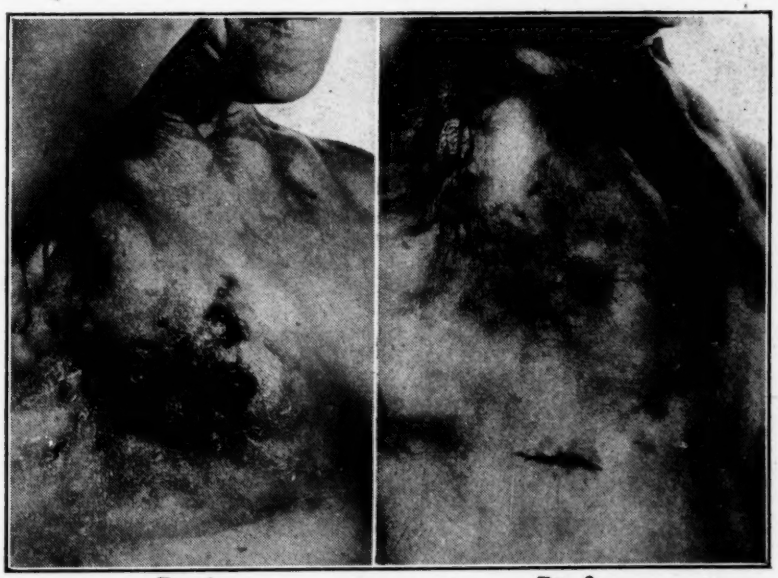

FIG. 1 FIG. 2

FIG. 1.—Cancer of the breast before treatment. FIG. 2.—The same case after oestrogen therapy.

established there is very little that is effective that can be done. Some firms are particularly skilful in making an elastic armlet which is light, serviceable, and comfortable (Fig. 3), and there is no doubt that this is the best method of treatment. It may be necessary to carry the arm in a sling, and an elevating arm-rest (Fig. 4) which may be fitted to any arm-chair and can be folded up gives great comfort. Massage and physiotherapy are helpful, but no operation has been devised so far which benefits this complication in any way. The prognosis is variable. The arm is generally a burden to the patient thereafter, but in a small minority of cases the condition improves spontaneously. If oedema of the arm appears for the first time months or years after the operation it may then be due to a recurrence in the axilla. Treatment by *x*-ray therapy will only make the oedema worse, and in most cases it is probably wiser to accept the inevitable.

FIG. 3.—Method of attachment of elastic armlet. (Reproduced by permission of the Editor of the *Leeds Medical Journal*.)

FIG. 4.—Folding arm-rest.

Isolated Superficial Recurrence.—It is unfortunately not uncommon for an isolated superficial recurrence to appear in the supraclavicular triangle, or in the skin of the chest wall. In view of the pathology of spread in cancer of the breast it is probable that these recurrences are indeed "isolated" in every sense of the term and they should generally be removed by surgery. Many patients survive indefinitely after this simple procedure.

The Last Days

The management of a patient dying from cancer is one of the most upsetting duties which a doctor is called upon to perform. Offensive lesions are best dressed with one of the many deodorant preparations now on the market. The patient's marked distress, as well as any pain from which she may be suffering, are treated by the prescription of a mixture containing ¼ gr. (16 mg.) of morphine hydrochloride and 1/12 gr. (5 mg.) of cocaine hydrochloride dissolved in two teaspoonfuls of water. Gin and lemon juice are added to taste and the mixture is prescribed as often as it is required. This preparation allays anxiety, ameliorates the pain, and imparts a little euphoria without making the patient fatuous or drowsy, so that she can converse with her family and even enjoy in a modest way her last hours in their company.

Next Refresher Course Article.—"Apoplexy," by Professor F. J. Nattrass.

BRITISH ORTHOPAEDIC ASSOCIATION

The spring meeting of the British Orthopaedic Association was held in Dublin during April 23–25, 1953, under the presidency of Sir REGINALD WATSON-JONES. Subjects discussed included transfusion, the use of an acrylic prosthesis for comminuted fractures of the radial head, club-foot, Pott's paraplegia, and the orthopaedic treatment of early poliomyelitis.

Dr. W. E. R. HACKETT (Dublin) discussed the advantages of transfusions of blood, plasma, and plasma substitutes before and during surgical operations. In anaemic patients who required transfusion before operation it was important that the blood should be given several days beforehand so that the body might benefit as fully as possible. Blood given during operation had its greatest usefulness in replacing blood lost. The risks of overloading the circulation by over-transfusion were small; a commoner error was not to give enough blood. With expert laboratory facilities reactions from mismatching were exceptional; in practice the only Rhesus factor of real importance was the D-antigen. So far there was no true substitute for blood. The best types of plasma substitute were the polyvinyl polymers such as "plasmasan" and the sugar polymers such as "dextran."

Professor L. E. WERNER (Dublin) recalled the significance of imbalance of the ocular muscles as a cause of tilting of the head in infants and young children. When due to an ocular imbalance such tilting could be corrected by an equalizing operation upon the eye muscles. In cases of torticollis, if an ocular defect was overlooked, orthopaedic treatment would be incompletely successful.

Mr. J. C. CHERRY (Dublin) had replaced the fractured radial head by an acrylic prosthesis in selected cases in which the head was badly comminuted. He described and illustrated the prosthesis and the special instruments used for their insertion, and gave details of the operative technique. Sir REGINALD WATSON-JONES (London) had no doubt that the operation was appropriate for the rare but definite cases in which fracture of the radial head was associated with rupture of the interosseous membrane and marked upward displacement of the radius.

Mr. A. T. FRIPP (London) discussed the treatment of relapsed or neglected congenital club-foot in children of from 6 months to 10 years of age. He had been impressed by his results with the Kite technique, in which wedged plasters are used: it aimed at gradual correction without harmful force and without anaesthesia. Each of the four components of the deformity (varus, inversion, equinus, and plantaris) was corrected successively by removing appropriate wedges from the plaster and closing the gap, the adjustments being made at weekly intervals. During treatment the foot became progressively more supple, and in most cases satisfactory correction was obtained.

Operative Treatment of Pott's Paraplegia

A discussion on Pott's paraplegia and its operative treatment was opened by Mr. H. J. SEDDON (London), jointly with Mr. D. LLOYD GRIFFITHS and Mr. R. ROAF. Mr. SEDDON described the pathology, prognosis, and indications for operation. Operation was indicated when paralysis had become complete; in all late onset cases; if continued improvement was not occurring under conservative treatment; when paraplegia was associated with uncontrollable spasms

of the legs; and if paraplegia recurred after initial recovery. Operation should be considered relatively early in older patients. Mr. D. LLOYD GRIFFITHS (Manchester) described in detail the operation of antero-lateral decompression as employed by Mr. Seddon, Mr. Roaf, and himself, and summarized the results in 48 patients on whom they had operated. Thirty-four recovered sufficiently to walk normally, eleven patients made little or no recovery, and three patients died. He emphasized that the operation was difficult and hazardous, and that patients should not be submitted to it unnecessarily. Mr. F. W. HOLDSWORTH (Sheffield) said that with the introduction of antero-lateral decompression our ideas on the treatment of Pott's paraplegia had been revolutionized. Mr. NORMAN CAPENER (Exeter) said that the operation he had described was essentially the same as that recommended by Mr. Griffiths.

Sir HARRY PLATT (Manchester) opened a discussion on the orthopaedic treatment of early poliomyelitis. The main problem was that of preventing and relieving crippling deformity. This could be tackled efficiently by the orthopaedic surgeon only if the patient came under his care at an early stage. Mr. D. M. BROOKS (London) declared that, in preventing deformity, the surgeon must remember its two causes—faulty posture and muscle imbalance. Faulty posture, which might be assumed in an attempt to minimize pain, was always preventable by appropriate splints. Muscle imbalance was more difficult to counteract, especially in children; when it was marked it was impossible to prevent deformity simply by external retentive apparatus. Relatively early tendon transplantation was often necessary. In general, it was true that if a muscle showed no sign of recovery within three months it was unlikely ever to recover.

Mr. J. I. P. JAMES (London) reviewed some of the features of Dupuytren's contracture. He recognized contracture of the fifth finger as a distinct clinical type in which the distal interphalangeal joint was not uncommonly involved. Subcutaneous tenotomy was occasionally justified in the elderly, but in the ordinary case excision of the palmar fascia through a skin-crease palmar incision and through midlateral digital incisions was recommended. The greatest hazard was oedema of the hand. Of 84 cases reviewed the result was perfect or good in 64, and fair or poor in 20. Metacarpo-phalangeal contractures could usually be overcome, whereas interphalangeal contractures were very liable to persist.

Colles's Fracture

Mr. W. DOOLIN (Dublin) opened a discussion on Colles's fracture of the wrist, with a sketch of the scientific, cultural, and social background against which Abraham Colles occupied with such distinction the chair of surgery in Dublin. Mr. G. N. GOLDEN (Guildford) reviewed the late results in 110 cases of Colles's fracture treated one to twenty years before. There was a definite and striking relationship between the quality of the reduction maintained and the results. It was suggested that more stable reduction and consequently improved results might follow the use of above-elbow plasters. Dr. W. R. HARRIS (Toronto) said that one of the difficulties was to maintain reduction. He and his colleagues in Toronto believed that the use of plaster-of-Paris was an inefficient method, especially in comminuted fractures. In selected patients a trial had been given to mechanical fixation by pin units of the Roger Anderson type. In 23 cases observed for from two months to five years after treatment there had been no recurrence of deformity and no patient had lost more than 5 degrees of wrist movement. In two cases the pin fixation had to be abandoned because of pin-track infection.

Mr. J. S. R. GOLDING (London) recalled that pain and tingling in the distribution of the median nerve in the hand were commonly due to compression of the median nerve behind the transverse carpal ligament. He had studied the clinical features and results in 50 patients subjected to operation. Most patients were women in middle life and the symptoms were bilateral in half. The results of decompression by division of the transverse carpal ligament were good.

Finally, Mr. W. GISSANE (Birmingham) paid a tribute to the memory of Edward Hallaran Bennett (1837–1907), a former professor of surgery in Dublin, who described the injury now widely known as Bennett's fracture.

POPULATION AND WORLD FAMINE

A new approach to the question of world food supplies and population was made by Professor J. B. S. HALDANE, F.R.S., when he addressed on May 2 the Medical Association for the Prevention of War. He took up certain recent statements about world population, in particular the address of the chairman of the British Association last year, which, he said, seemed to take it for granted that animal species in general were limited in their numbers by famine. He contested the assumption that there was an inevitable tendency for species to increase beyond their means of subsistence. This was true only in very exceptional instances. Professor Haldane cited several examples from biology concerning the various factors which regulated animal population, and he claimed that in the vast majority of cases death in the animal kingdom could not be put down to the exhaustion of the available food by animals of the same species. Insect populations were usually limited by disease, bird populations by the territorial system which prevented one pair from nesting too close to another and thus put a limit on egg production. This biological fact made one a little dubious about the prophecies concerning the future of the human species and the limitation of population by food shortage.

Professor Haldane took the case of India. It could certainly be said that India was over-populated, but equally that it was under-irrigated. If India were properly irrigated and drained it could produce enough food to provide a comfortable existence for its people. But the prophets of gloom would say that in such an event the population would increase beyond all bounds so that starvation would be nearer than ever. The answer was that it would be impossible properly to irrigate India by primitive dam-making methods; it was work which called for modern engineering techniques, and would result in India becoming to a considerable extent industrialized; and it was the general experience that industrialization, after a certain lag, led to a considerable fall in the birth rate. It could be hoped that as Asiatic countries became industrialized the birth rate would fall as it had fallen in European countries and in Japan. That event was much more likely than an indefinite increase in population.

Food Shortage in Britain

In Great Britain, Professor Haldane continued, the position was much more interesting. We were not producing as much food as we needed, and we were finding it harder to import. It might be that India would get out of a cycle of famines, and Western countries get into it. Up to the present our food materials were almost invariably materials which had been available to neolithic man. But a large number of valuable sources of synthetic foods might await the organic chemist. True, the money needed to establish the first synthetic fat factory might be of the order of magnitude of that required to establish a factory for making atom bombs, but it would be a safer investment. All the steps in fat synthesis were in principle known, but each one of them at present was extremely inefficient and expensive. It was unfortunate from one point of view that neither the United States nor the Soviet Union had any food shortage in prospect in the near future, because therefore their scientists were not interested in food production from new sources. Under neither of the two predominant ideologies would much thought be given to this subject at present, and therefore it was for Great Britain and India and other countries under the shadow of food shortage to make their respective Governments aware of the fact that this was a problem not likely to be solved on either American or Soviet initiative, and yet one which was not insoluble.

THE CHANGING FUNCTION OF HOSPITALS

PROFESSOR VINES'S ADDRESS TO HOSPITAL ADMINISTRATORS

The suggestion that perhaps the National Health Service, like other national services, was getting a little "hag-ridden by administration" was made by Professor H. W. C. VINES, of Charing Cross Hospital, in an address which he delivered to the annual conference of the Institute of Hospital Administrators at Hastings on May 9. He confessed himself rather tired of these massive hospital accounts and statistics, which, however excellent they might be in demonstrating a saving to the Exchequer, were quite uninformative about the real work of the hospital, which was the care of the patient and the control and prevention of sickness.

Traditionally, said Professor Vines, the hospital was the main centre of curative medicine, and there were few hospitals which had not a sound or even a brilliant record in that respect. But a hospital was also a place for investigation into the causes of disease and methods of treatment. Given a little co-operation between the hospital and the general practitioner, the result of what was done in the hospital should be easily accessible to patients in their homes. The hospital was a place to which the general practitioner could refer patients, but it should also be a place of welcome resort for general practitioners where they could gain knowledge and experience in the newer techniques of patient care. This was vital to the future of the Health Service. The nationalized hospital must become the structural and functional embodiment of the national policy for the management of the sick, but at present it was not very obvious that there was any particular policy of medical care. The long-term programme should be to empty the hospitals rather than fill them. Medicine to-day was concerned primarily with the cure of disease or the patching up of tissues, but it should become increasingly preventive in its aim.

The Cult of the Bed

Too many administrators had been brought up in the belief that the importance of the hospital lay in the number of beds it contained and in the care of its in-patients. This cult of the bed should be replaced by a more balanced outlook in which all the services a hospital could offer were seen in perspective. The out-patient more often than the in-patient offered a chance of prevention, and at the same time the patient, while undergoing investigation and treatment, remained in his normal way of living and perhaps at his job. If patients could be persuaded to seek advice about their illness a good deal earlier hospitalization might become less necessary.

In many hospitals the out-patient was apt to be put on a lower plane than the in-patient, and to be regarded as a necessary evil except in so far as he had a potential value as a future occupant of a bed. On the in-patient was lavished much thought and care. Structural planning had the in-patient in view. But the accommodation of out-patients was low on the list of expenditures, and the out-patient department was generally too old, too small, and too crowded for efficient work. The ancillary facilities for thorough and rapid diagnosis were often inadequate. Such conditions positively encouraged the admission of patients to beds for examination, to the interruption of their normal lives and the increase of public cost. The upgrading of the out-patient service would offer a suitable field for the exercise of real preventive medicine.

Importance of the Out-patient

The hospital service, Professor Vines continued, already took over half the hard cash allowance of the National Health Service. Financial stringency, they were given to understand, was extreme. No new major hospital had been built for fifteen years. Almost daily there were pleas for reduction of expenditure. Charges were put on essential items in the free medical service. The future of the hospital service, in his view, could not lie along the unimaginative line of building more and more beds for ever and ever. Under conditions of financial difficulty it would perhaps be better to write off the greater number of these hypothetical beds, and to fill the gap by allowing the beds to recede a little and the out-patient clinic to come forward to a place of at least equal importance.

By earlier diagnosis it should be possible to reduce the "no man's land" between health and disease, now represented by the time-lag between the patient's admission to himself that he was not well and his positive action in seeking medical advice. In diagnosis the first step lay with the patient, and he must be persuaded to take that step earlier. At the same time the medical profession would need to develop a more inquisitive outlook towards the less obvious signs of ill-health and develop more delicate diagnostic tests. By thus preventing the advance of physical deterioration, a higher proportion of patients would be ambulant and would have a better chance of remaining so. The number of beds might be lessened, but the volume of work in the out-patient clinic would be increased.

The future of the hospital might lie in the polyclinic. Existing out-patient clinics must be completely overhauled. He envisaged a complete range of general and special clinics in the largest of the hospitals grading down to clinics only in general medicine and surgery in the smallest. But no hospital should be allowed to have out-patient services which did not have facilities for radio-diagnosis and pathology on its premises. To save the time of the patient, and incidentally of the staff, these facilities must be sited in relation to the clinic so that the patient could be given the most thorough diagnostic examination at one visit instead of being frequently recalled for these ancillary examinations. This was the challenge of the future. The new inquiry into the costs of the health services might well be enlarged to become an investigation into the whole structure and effectiveness of the Service. Infinite harm might result from a too facile application of economies which saved the Exchequer at the expense of the patient's well-being.

LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE

At the annual meeting of the Court of Governors of the London School of Hygiene and Tropical Medicine on May 6 Sir COSMO PARKINSON from the chair said that they all felt honoured by the fact that the Duke of Edinburgh had consented to become Patron of the School. Referring to the annual report, Sir COSMO PARKINSON said that he had been struck by the variety as well as the quantity of work going on in the School, and by the amount of basic research and specific inquiry being undertaken in addition to the normal teaching. He welcomed the fact that the staff also served on Government committees, boards of management of hospitals, and in an advisory capacity overseas.

Dr. ANDREW TOPPING, the Dean, said that he and his staff welcomed students from all over the world, many of whom made the School their first place of call on arrival in this country. There had been during the year under review 71 students taking the D.P.H. course, and of that number all except 10 had been sent by colonial administrations, by the Services, or by other organizations, national and international. Fewer students took this course now than was the case before the war. Naturally the fees did not nearly cover the cost of the tuition given, and he was a little worried that the British taxpayer should indirectly be paying for tuition to be given to students from some countries who did not speak very nicely about us. Sometimes it was simply a matter of "diploma collecting."

Mr. A. R. WOOD, the Joint Honorary Treasurer, regretted having to report that expenditure had exceeded income by some £7,000. Eighty-five per cent. of their income represented Government grants; only 5% came from fees. They had in mind various economies which they hoped to put in hand, without having to curtail the present activities and scope of the School.

Correspondence

Smoking and Cancer of the Lung

SIR,—If we accept the main conclusions of Dr. Richard Doll and Professor Bradford Hill,[1] and, further, accept also their estimates of the various risks of dying from cancer of the lung according to the number of cigarettes (or their equivalent) smoked, we can in rough terms express the risk that a young man takes when he is about to set out on a career of smoking. It is one thing to demonstrate a relationship between smoking and lung cancer—quite another to give a quantitative estimate of the risk of dying as a function of the amount smoked. It would, for instance, be of academic interest if a lifetime of smoking increased a man's chance of dying of lung cancer from one in a million to one in a hundred thousand. It would not be so academic if it could be shown that the risk was increased from, say, 1 in 300 to 1 in 10.

As we see it, the young intending smoker-in-the-street, if he is a thoughtful and calculating type, would want to know what difference it makes to his chances of dying from cancer of the lung if he smokes a given number of cigarettes a day, and will this difference add noticeably to the chance of his early demise?

Since the authors of the paper have been able to make provisional estimates of the risk of dying in any one year according to age and amount smoked, we have taken the bait. Using the life-table approach, as we did when estimating the chances that medical practitioners would get coronary heart disease (Morris and ourselves[2]), we have estimated the number of men, out of a thousand aged 25, who would die (*a*) of lung cancer, and (*b*) of other causes, before the ages of 55, 65, and 75 respectively, if they did not smoke, if they smoked 15–25 cigarettes per day, and if they smoked 25–50 cigarettes per day. In doing this we hasten to add that we are aware that our results can be no more dependable than the estimates on which they are based, and are probably rather less so for reasons which we discuss below. We feel, however, that, given the estimates, the answers we get are reasonable. The results are given in the table below, which relates, as do the original estimates, only to Greater London, where lung cancer mortality is rather higher than in the rest of the country.

Age (Years)	Of a Thousand Men Aged 25, the Following Numbers can be Expected to Die Before the Stated Age								
	Non-smokers			Smoking 15–25 Cigarettes per Day			Smoking 25–50 Cigarettes per Day		
	From Cancer of the Lung	From Other Causes	From All Causes	From Cancer of the Lung	From Other Causes	From All Causes	From Cancer of the Lung	From Other Causes	From All Causes
55	1	130	131	15	128	143	22	127	149
65	2	298	300	32	292	324	54	288	342
75	3	577	580	52	557	609	90	541	631

The index of smoking used is the "average amount of tobacco smoked daily in the preceding ten years." Since the rates quoted in the paper are based on the population of Greater London in 1950, the death rates from causes other than cancer of the lung are taken from the same population. The method of calculation used was a rough graphical graduation of the rates of death in the age groups given in the paper, from which we deduced rates for five-year age groups and constructed a life table.

For Londoners smoking 15–25 cigarettes per day the risk of dying from cancer of the lung before each of the three ages 55, 65, and 75 is about one-tenth that of dying from all other causes; for those who smoke 25–50 cigarettes per day it is about one-sixth. The chance of dying from cancer of the lung before the age of 55 for the men who smoke 15–25 is about 1 in 70, and about 1 in 50 for those who smoke 25–50 (i.e., 15 and 22 in 1,000), while the corresponding risks of dying before 75 are about 1 in 20 and 1 in 11. For men who do not smoke the chance of dying from cancer of the lung is about 1 in 1,000 before the age of 55 and 1 in 300 before the age of 75. Further, on the basis of these figures a man increases his total chances of dying from all causes before 55 by about one-seventh (i.e., by 18 from 131 to 149) if he smokes 25–50 cigarettes per day or its equivalent, and his chance of dying before 75 by about one-twelfth. At this heavy level of smoking of 25–50 cigarettes per day, the risk of death from cancer of the lung for men aged 45–64, among the general male population of Greater London, is greater than the risk of dying from all other cancer put together or from coronary heart disease.

To arrive at these figures it was necessary to make two major assumptions over and above those made in the paper, perhaps the most important of which was that, because of the very high mortality from the disease, the authors equated the risk of dying from lung cancer with the risk of getting it. The first new assumption is that the smoker and the non-smoker are subject to an equal risk of dying from causes other than cancer of the lung—and that this risk can be assessed from the death rates from causes other than cancer of the lung in the general population—which includes, of course, all smokers and non-smokers. It is possible that, at any given age, the non-smoker suffers a slightly greater risk of dying from causes other than cancer of the lung than does the smoker, because the men who would have died of cancer of the lung had they smoked are now subject to the risk of dying from other causes. This extra risk must, however, be small. Moreover, it is conceivable that smokers are subject to greater mortality risks than non-smokers from causes other than cancer of the lung (other respiratory conditions, for instance), and this would tend to counterbalance the other effect. So far the argument applies to the risk at a given age. The cumulative effect, for the ages 25–75 covered by the table, is evident in the calculation. Because non-smokers have fewer deaths from cancer of the lung, more of them survive to the later ages. This greater number is, however, subject to the risk of death from causes other than cancer of the lung equally with the smokers. As will be seen from the table, the result is that, although the number of deaths from all causes is smaller, the number of deaths from causes other than cancer of the lung is greater among non-smokers than among smokers.

The next assumption is about the risk of death from cancer of the lung among non-smokers. The figures in Doll and Bradford Hill's paper are based on very small numbers for non-smokers, and the authors themselves, of course, do not place any reliance on the precise value of the rates. Dr. Doll has, however, very kindly given us the estimates of the rates for non-smokers which he made in his Milroy Lecture.[3] These estimates are based on much larger numbers, but include women as well as men, and apply to all the areas in the inquiry, not merely Greater London. Dr. Doll showed that there was good reason to believe that lung cancer rates for non-smokers were no greater for men than for women, or for Greater London than for the rest of the country. We have therefore used his rates as the basis of our estimates for the men of Greater London who do not smoke. If these estimates were doubled it would make very little difference to the figures for non-smokers or the comparisons we have made.

The methods used throughout are approximate, and no more is claimed than that the figures are a reasonable attempt, in the light of present knowledge, to answer the two important questions mentioned earlier. They are of course subject to any possible improvements in therapy which may affect the basic assumptions, for the calculations are based, as in most life tables, on present rates. Moreover, it may be that something has to be associated with smoking before it is lethal, and that this something can be removed or modified; or it may be possible to change methods of smoking, or the tobacco itself, and so reduce the risk. A third question which the investigation cannot answer, but which is at least as important, is: "If a man aged, say, 50 has been smoking heavily for 30 years, and now gives up smoking, what difference, if any, will it make to his chances of dying from cancer of the lung?" Perhaps future papers by Dr. Doll and Professor Bradford Hill will tell us the answer.

In order to avoid bias in the calculations, the writers of this letter were selected on a random basis so that 50% of us is a smoker. We are grateful to Dr. J. N. Morris for criticisms and suggestions.—We are, etc.,

J. A. HEADY.
R. G. BARLEY.

London, W.1.

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2 Ibid., 1952, 1, 503.
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Chemotherapy of Malaria and Trypanosomiasis

SIR,—It is fortunate that in my paper on "The Chemotherapy of Malaria and Trypanosomiasis" (*Journal*, February 7, p. 311) I omitted to mention the effect of pentamidine in *Trypanosoma rhodesiense* sleeping sickness, because this omission has stimulated Dr. A. J. Keevill to put on record his own experience in the matter (*Journal*, May 2, p. 993). If it is true that nearly all textbooks fail to differentiate between the treatment of infections due to *T. rhodesiense* and *T. gambiense*, it is surely because those with experience of the use of pentamidine against *T. rhodesiense* have been too modest to publish their findings. Dr. E. M. Lourie has written on several occasions complaining of this lack of information,[1 2] the only reports available being couched in general terms and devoid of clinical data. Dr. M. A. de Andrade Silva presented details of recent work in Mozambique to the meeting of the International Scientific Committee for Trypanosomiasis Research held in September, 1952.[3] In this paper, which was published only a few weeks ago, he reports that pentamidine isethionate proved to be successful in 22 of 25 acute *T. rhodesiense* cases; trypanosomes in the blood decreased in numbers within 16 hours and disappeared in all cases within 28 hours of the first injection. The remaining three patients died, one from unknown causes, one from trypanosomiasis of the central nervous system, and the third from unchecked, acute trypanosomiasis. This last case would appear to resemble those reported by Dr. Keevill. De Andrade Silva also reports that in more advanced cases from an area in which suramin–tryparsamide treatment had given a high proportion of failures the substitution of pentamidine–tryparsamide proved to be more effective.

It is clearly time for this subject to be ventilated. In localities where suramin is completely satisfactory, both from the point of view of the control of the acute infection and the prevention of relapses, there can be, as Dr. Keevill says, no justification for a change. Also, where the incidence of infection is low, there is no case for widespread prophylactic chemotherapy. However, strains of trypanosome often vary in their sensitivity to a drug—Dr. Andrade Silva's cases were more sensitive to pentamidine than Dr. Keevill's—and it is possible that in some areas there may be cases which respond less satisfactorily to suramin than to pentamidine. It would be most interesting to obtain further evidence on this point.

In any event it would seem to be worth while trying the combination suramin–pentamidine suggested by Guimaraes and Lourie,[4] which should combine the trypanocidal actions of the drugs and also minimize the toxic side-effects of pentamidine which have troubled workers in East Africa in the past.[5]—I am, etc.,

London, N.W.1. L. G. GOODWIN.

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Incidence of Scabies

SIR,—I was interested, but not surprised, to read Dr. Allan Bigham's observation (*Journal*, April 25, p. 941) regarding the increased incidence of scabies. This infestation has long been considered to be venereal in origin.

In the third quarter of last year I first noted a rise in the incidence of gonorrhoea. Similar rises in other clinics in the Manchester region lead me to think the new incidence levels are probably connected with the unemployment in the cotton industry coupled with the increased shipping arriving at Manchester Ship Canal (the tonnage for 1952 was a record for this port). However, not only has the increased gonorrhoea rate been maintained locally into the first quarter of 1953, but it has come to be known that the rise in gonorrhoea has been on a national scale. Like scabies, the gonorrhoea incidence rose first prior to the last war (I do not know the rates prior to the first world war). I am confident, therefore, that Dr. Bigham's observation will be confirmed up and down the country.

It is interesting to speculate why these predominantly venereal diseases should suddenly become commoner. Is it possible that they reflect a sense of national insecurity which makes for greater dominance of the herd instinct, many of the ensuing temporary friendships reaching the sexual level?—I am, etc.,

Stockport. R. S. MORTON.

SIR,—Scabies has been notifiable in London for some years. The number of cases has fallen progressively in the borough of Lambeth, from 851 in 1945 (population 173,000) to 36 last year, 1952 (population 229,000). The increase during the war has been attributed to shelter life and the generally unsettled conditions which existed at that time. Modern methods of treatment have played a great part in reducing the incidence.—I am, etc.

London, S.W.2. A. G. G. THOMPSON.

Heart Disease in Pregnancy

SIR,—Professor Crighton Bramwell's excellent article (April 25, p. 897) on heart disease in pregnancy, which I have studied with great profit, omits one type of cardiac deficiency which I have observed relatively frequently in pregnancy. In the type of case I have in mind tachycardia with oedema of the legs and dyspnoea appear in the later weeks of pregnancy. There may also be cyanosis, especially malar cyanosis, which in some cases is quite marked. Examination may show slight dilatation of the heart, but no evidence of any valvular lesion. Once the pregnancy is over all signs and symptoms disappear, but during the last weeks of pregnancy rest in bed may be necessary, and towards the end of labour even the administration of oxygen in order to diminish foetal anoxia may be indicated. Normal labour is usually possible, but a forceps delivery may be desirable if the second stage is prolonged or difficult.

I believe that these cases constitute a definite entity and that the underlying lesion is a chronic myocarditis dating from a rheumatic infection in early life. The heart is perfectly adequate for ordinary living, but the increased load in pregnancy with the demand for raised cardiac output and the mechanical embarrassment due to upward displacement of the diaphragm by the gravid uterus are reflected in the symptoms of mild deficiency which I have described. The condition appears to be analogous to the so-called "low reserve kidney" described by Stander as the underlying cause in certain cases of pregnancy toxaemia. I think it is important that the condition should be recognized, since it displays few of the clinical signs described by Professor Bramwell in his paper.—I am, etc.,

Worcester. J. A. CHALMERS.

SIR,—The dissertation by Professor Crighton Bramwell upon the hazards of pregnancy in women with heart disease (*Journal*, April 25, p. 897) is a welcome contribution to our knowledge of the prognosis of cardiac cases in pregnancy. It also casts a good deal of light on their prospects afterwards. In so far as it is a survey of work done and data collected, it is complete. However, we feel that this is a useful occasion to stress the desirability of admitting these cases prior to delivery for a period of rest and observation. This does not apply with quite the same force to Group I, but certainly cases in the other groups should be admitted if this is at all possible. Antenatal beds are now available more generally, and a very real opportunity exists for obstetricians to assess and treat cardiac patients at a particularly important time.

Some of this work loses much of its point unless such cases are carefully followed up, and this, we feel, is more appropriately accomplished in medical out-patients.—We are, etc.,

F. C. RUTTER.
Watford. J. N. JACKSON.

Transverse Arrest of Head

SIR,—All who practise obstetrics are indebted to Mr. Bryan Williams for his clear exposition (*Journal*, April 18, p. 865) of the problems associated with transverse arrest of the head and for the differentiation of this condition from a persistent occipito-posterior position.

With reference to the use of Kielland's forceps, Mr. Williams puts the matter fairly when he says that it is "no more or no less dangerous than any other one," but it seems to me regrettable that he should give the impression that transverse arrest of the head can only be dealt with adequately by those who have mastered the use of this instrument. No one will deny that in the hands of an expert the use of Kielland's forceps gives most excellent results, but in a rural area the standard of domiciliary obstetric service by general practitioners must of necessity be high, and I do not think that an experienced practitioner should feel himself debarred from dealing with a case of transverse arrest because he has not got a pair, provided other facilities, particularly an anaesthetist, are available. Once he has understood the technique of manual rotation, which involves rotation of the shoulders as well as the head, and is beautifully described by Munro Kerr, he will find that his old and trusted forceps will provide an equally satisfactory result. I cannot agree that manual rotation necessarily demands deep general anaesthesia. In hospital practice I employ low spinal anaesthesia or epidural block for preference.

Whichever procedure is adopted, success depends on a clear understanding of what one is trying to do, and it is in this respect that Mr. Williams's contribution is so helpful. —I am, etc.,

Norwich. A. P. BENTALL.

SIR,—In his article (*Journal*, April 18, p. 865) Mr. Bryan Williams stated that in true occipito-posterior positions a deliberate face-to-pubes delivery is usually indicated when the head is low and that this has a small foetal risk. He quotes 63 cases treated in this way with four foetal deaths.

At University College Obstetric Hospital the criteria for deciding how to deliver a posterior position of the occiput do not differ greatly from those outlined by Mr. Williams; but the figures from 1944 to the present time suggest that manual and forceps rotations of the head carry less risk for the foetus than a forceps delivery face-to-pubes. In addition no one can deny that the attendant who is not experienced in forceps delivery face-to-pubes may add the complication of a complete tear.

	Cases	Foetal Mortality
Manual rotation and forceps delivery ..	88	3 (1 admitted as a "failed forceps")
Rotation and delivery with Kielland's forceps	11	0
Delivery with forceps face-to-pubes ..	38	3

Figures can be misleading, and a group of cases delivered face-to-pubes may contain some in which the operator was unable to rotate the head and used excessive force to extract the child face-to-pubes. Mr. Williams is undoubtedly right that forceps delivery face-to-pubes is the best way to deliver a woman when the foetal head is low and the pelvis anthropoid, but his overstressing of the dangers of manual and forceps rotations of the head may discourage accoucheurs from performing them at the proper time.—I am, etc.,

London, W.C.1. J. D. MARTIN.

SIR,—Mr. Bryan Williams's paper (*Journal*, April 18, p. 865) on transverse arrest and the occipito-posterior position merits the most careful study, and I cannot recall an obstetrical paper which has afforded me greater pleasure and with which I found myself generally in such full agreement. Although Mr. Williams makes it quite clear that the problems of transverse arrest and occipito-posterior are two entirely separate problems, it is, perhaps, a pity that he proceeds to consider both subjects. I shall confine my comments to his points on transverse arrest.

"While American and Continental obstetricians lay stress on its [transverse arrest], however, it receives inadequate attention in this country. . . ." This is only too true. Mr. Williams's paper is the first major report on this condition in Britain since Shaw.[1] The reason appears to be that Kielland's forceps have never publicly received the attention they merit in this country, and without their use transverse arrest is indeed a problem. The reason is due to the danger of the classical method of application of the anterior blade. To this, Mr. Williams has found the answer: "The classical method of rotating the anterior blade of this instrument inside the uterus cannot, however, be free from risk either to the baby or to the uterus and anterior vaginal wall, and is nowadays unnecessary. This blade can be passed into position over the face by a wandering, gliding, or migratory movement." This statement is the most significant in Mr. Williams's paper. It is usually surprisingly easy to carry out this manœuvre, and I am sure it requires the widest publicity for those obstetricians who have, to date, avoided the use of Kielland's forceps or who have only used the classical application. I stress this, for, although for many years I used Kielland's forceps with the classical application without untoward result, the potential danger was always there, and I am quite sure that their classical use by the "occasional obstetrician" is to be condemned. I experimented extensively to try to overcome this difficulty, including getting Chas. Thackray's to make some Kielland's forceps, with ingenious and beautifully constructed hinges at the neck of the blades, so that the anterior blade could be applied direct under the symphysis. Although these proved successful, a study of Smellie's works (to whom Mr. Williams pays tribute) suggested the simple procedure described by Mr. Williams, and I have now been using this method for some time, with no difficulty. The only other reference I can find in modern literature is a mention of this method by Greenhill.[2] Chassar Moir[3] describes the anterior blade being applied to the sacrum and being rotated through 180 degrees, but the 90 degrees rotation is all that is required and is easier.

"The application of forceps to the non-rotated head should be carried out only by those of experience." Although I do not wish to minimize the difficulties of some cases of transverse arrest, I hope—and do not believe—that Mr. Williams wishes to exclude the general-practitioner obstetrician from the use of Kielland's forceps. With the new method of application of the anterior blade, the Kielland's forceps—to quote Mr. Williams—"is no more or no less dangerous than any other one." In a series of 50 cases of transverse arrest, I found that in two-thirds of the cases the delivery was easy. The difficult one-third can be diagnosed, as a rule, by careful pelvic examination, the degree of moulding, the size of the caput, the uterine contractions, etc., and, for these, general practitioners would be wise to call in consultant aid.

I have given up the use of manual rotation in cases of transverse arrest. It is not usually as easy to do as the textbooks suggest. If it is easy, then it is even easier to do with the forceps, and involves less manipulation and less chance of incorrect application of the blades. It may, as Mr. Williams points out, be positively harmful, as in many cases rotation should not be performed until the head is at a lower level. As regards diagnosis of transverse arrest, in nine cases out of ten it can be correctly diagnosed over the telephone, without seeing the patient. If the cervix has been fully dilated for one and a half to two hours, and no part of the head is visible at the vulva, it will nearly always be a case of transverse arrest.

The aetiology of transverse arrest requires more study. It is far more common in primigravida (45 out of 50 in my series). It hardly ever recurs in the same patient at a subsequent pregnancy. In about 75% of cases uterine inertia or abnormal uterine action was the prominent feature. —I am, etc.,

Harrogate. C. RUTHERFORD MORISON.

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Vomiting in Late Pregnancy

SIR,—I wish to dissent from what I believe to be the dangerous view expressed by Dr. Samuel Lask in his article "Treatment of Nausea and Vomiting of Pregnancy with Antihistamines" (*Journal*, March 21, p. 652). He states: "It is occasionally taught that vomiting late in pregnancy is of serious significance, but in the absence of any evidence of pre-eclampsia this is not so."

Is it not just this belief that is, in the main, the explanation for the higher mortality of the acute abdomen in pregnancy than in the non-pregnant? Because a women is pregnant, the vomiting that in a non-pregnant person would have led to careful investigation is ignored as being an unfortunate coincidence. This attitude leads to dangerous delay in diagnosis, one of the most important factors in the higher mortality. Such a view, as expressed by Dr. Lask, must inevitably lead to delay in diagnosis.—I am, etc.,

London, E.C.1. R. A. STRUTHERS.

Post-partum Haemorrhage

SIR,—The paper by Drs. J. D. Martin and J. G. Dumoulin (*Journal*, March 21, p. 643) on the "Use of Intravenous Ergometrine to Prevent Post-partum Haemorrhage" is of great importance, for post-partum haemorrhage is too common. Much was achieved when the midwife was allowed to use the drug when a haemorrhage had occurred. We should find out if this is sufficient, and if its use should be advocated before the third stage is complete.

During the past three years at the British Hospital for Mothers and Babies, work of a similar nature to that described has been carried out, although we have been using 1 mg. ergometrine or "methergin" (methyl ergometrine) intravenously. The aim has been to give the injection when the shoulders are born. Sometimes if the midwife is virtually single-handed the injection has had to be delayed till the baby is born and separated. Alternate cases have been used as controls, and this comment refers to an experience of 1,130 patients.

In the ergometrine or methyl ergometrine group (565) there were 26 (4.6%) haemorrhages of 20 fl. oz. and over (over half a litre). Nineteen of these were in the methyl ergometrine group and seven in the ergometrine group. In this same group the placenta was manually removed on 21 occasions (3.7%). The vast majority of the third stages were completed in five minutes.

In the control group (565) there were 57 haemorrhages (10%). The placenta was removed on nine occasions (1.6%). The bulk of the third stages were completed in 20 minutes, and almost all in 30 minutes.

Post-partum Haemorrhage fl. oz. (litres)	Number of Cases		
	Ergometrine	"Methergin"	Nil
0–29 (0·57–0·82)	2	8	32
30–39 (0·85–1·11)	2	5	13
40–49 (1·14–1·39)	3	4	9
50–59 (1·42–1·67)		1	2
60–69 (1·7–1·96)		0	0
70 (1·99)		1	1

Our figures show that haemorrhage can be reduced by 50% if ergometrine or methergin is given intravenously, but in a series the manual removal rate was more than twice as great—1.6% to 3.7%. In short, they exactly confirm the important work carried out at University College Hospital by Martin and Dumoulin.—I am, etc.,

London, S.E.3. KEITH VARTAN.

The Backward Child

SIR,—I should be grateful for permission to comment on Dr. Lise Gellner's letter (*Journal*, April 25, p. 936), in which she outlines her views on the causation of mental defect. She suggests, if I understand her correctly, that mental backwardness is caused by lesions situated in the geniculate bodies.

In the course of the last few years I have been able to examine over 100 brains and spinal cords of mentally defective children, chiefly of lower grade. Some of these brains were studied in considerable detail; all were carefully examined macroscopically, dissected, photographed, and prepared for future histological examination. This work is being continued, and I hope to present the results more fully at a later date. The evidence emerging from this material so far lends no support to Dr. Gellner's hypothesis. It is true that lesions situated along the course of the veins of Galen were present in certain cases, and I have reported one of them with the suggestion that it was caused by birth injury.[1] Such lesions were, however, the exception rather than the rule, and were never the sole ones in the affected brains. The geniculate bodies were, moreover, spared in the case referred to above, and this is, I believe, the usual finding.

Every brain in our series presented some structural abnormality, and my impression is that the most conspicuous and common lesions were situated in the cerebral cortex adjoining white matter. These lesions took many different forms, indicating possibly such diverse causes as infection, birth injury, and abnormal development. The most common single abnormality was the smaller weight and size of the brain, or certain of its parts, although this was often masked by associated hydrocephalus and oedema. The corresponding changes in histological sections consisted mainly in patchy or diffuse, generalized or localized, reduction in the number of nerve cells with or without gliosis or cystic degeneration. It is my belief that the reduction in weight was mainly at the expense of the cerebral hemispheres, although other parts of the nervous system such as the cerebellum or spinal cord were in some cases relatively smaller than the cerebrum. I have not, on the other hand, seen any case in which the geniculate bodies were selectively involved, although the lateral geniculate bodies were abnormal in several cases of microphthalmia which showed also atrophy or lack of development of the optic nerves, chiasma, and optic tracts.

In view of these findings it is hardly necessary to discuss the theory that visual and auditory impulses are integrated with interoceptive ones from the hypothalamus in the geniculate bodies, and that this integration is specially related to the development of intelligence. Such evidence as exists on integration as a basis for intelligence is chiefly derived from Pavlov and his school, and points to the cerebrum as the organ of the highest integration, and therefore of the mind. Pavlov's studies have likewise demonstrated in a very striking manner the plasticity and power of compensation inherent in the brain. He provided, furthermore, a physiological basis for this plasticity in his theory on the arrangement of the nuclear and peripheral parts of the cortical analysers. Dr. Gellner is therefore perfectly justified in attempting the development of the dormant intellectual potentialities of children in her care, and I should like to wish her well in this, even though it is impossible to agree with her theoretical postulates.—I am, etc.,

London, S.W.17. L. CROME.

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Myxoedema as a Cause of Death

SIR,—"The fish that got away is often the best." The following case adds point to the article by Dr. Le Marquand and his colleagues (*Journal*, March 28, p. 704), because the patient, who had been given up as hopeless, made a complete recovery from deep coma in advanced myxoedema.

The patient, a married woman aged 84, had suffered from a variety of symptoms ascribed to old age, which had gradually increased in intensity over a period of many years. They included dyspnoea on exertion, swelling of the ankles, puffiness of the face, increase in weight, deepening and roughening of the voice, intolerance of cold, deafness, chronic post-nasal catarrh and cough, retardation and dulling of mental processes, and drowsiness and dysarthria, the latter apparently associated with swelling of the post-nasal adenoid tissue. Dryness of the skin with loss of scalp hair and eyebrows was also noticed. The drowsiness became so pronounced that the patient would fall into deep sleep in the middle of a conversation or during a meal. Sleep

at night was accompanied by such sonorous snoring that other members of the household were wakened and kept awake by it.

Though myxoedema had been considered, thyroid had been given only occasionally for short periods and in very small doses. But intensification of the drowsiness prompted further investigation. At this stage one of us noted, among others, the following signs: oedema of the ankles, puffiness of the face, especially the eyelids, cold extremities, scanty scalp hair and eyebrows, oedema of the post-nasal space, a loud systolic aortic murmur, raised blood pressure, Cheyne–Stokes type breathing, a swelling of the abdomen which was apparently fluid and thought perhaps to be an ovarian cyst. The urine contained pus and *Bact coli*. But of the profound myxoedema there was no doubt. The patient was accordingly given thyroid gr. ½ (32 mg.) twice a day, though any response seemed unlikely. Within two days the drowsiness had deepened into coma from which she at first could be roused, but after another 24 hours she was unrousable and became incontinent of urine and faeces. After a day or two in this coma she was moved into hospital. After a further three days the coma became less deep, and more thyroid was given by mouth. From then on recovery was slow but complete, and the patient is now stabilized on 2 gr. (0.13 g.) of thyroid daily. Higher doses produce discomfort and sleeplessness. It is now eighteen months since the patient was in hospital, when no one believed that she could live more than a few days. She had reached the same conclusion, and her recovery was as unexpected to her as to those who were caring for her. She has now for over a year been back at work in her home, alert, cheerful, and active for her age. The deafness and all the other symptoms have either disappeared or become of no account. The oedema cleared early. Her features, from being puffy and pale, have become sharp and of good colour. Hair has grown on the scalp, and it is brown, not grey. Her mental activity, wit, and power of repartee have returned. The change is so remarkable that she now looks as she looked 15 years ago, and for the first time for 40 years she does not feel the cold.

All those concerned regard this virtual return from the grave to a brisk and active life as nothing short of a miracle: and so indeed it may be. Thyroid was the only drug given except iron and pot. citrate, and yet the very varied signs and symptoms disappeared, including the urinary infection with its associated frequency of micturition. The slow response to thyroid medication in the first few days of deepening coma is worthy of note and needs underlining, because failure to persevere would certainly have ensured the patient's death.

We strongly suspect that we are often in danger of missing myxoedema, especially in those of advanced years. The changes are so insidious and so gradual that those near the patient—relatives and medical advisers alike—can hardly be blamed for failing to notice them, or for regarding them as usual accompaniments of old age. But in a patient seen for the first time the picture is quite unmistakable—otherwise this case might well have been a third fatality to add to Dr. Le Marquand's two.—We are, etc.,

LAURENCE MARTIN.
C. HOWARD WHITTLE.

Cambridge.

The College of General Practitioners

SIR,—As one who in 1905 started medical work as a general practitioner, I have been interested in the suggested formation of a College of General Practitioners. Since July 5, 1948, as vice-chairman of the General Health Services Board in Northern Ireland, which corresponds to an executive council in Great Britain, I have been closely connected with the work of family doctors.

One of the objects of the new College is, I believe, to raise the status and prestige of general practice. If, in fact, this is now necessary I ask myself why these appear to have fallen so strikingly since 1948. As I see it, it has come about from the almost universal rush of the community as a whole to their doctors when they were told that they were getting this service free. This demand (much of it unjustified) on the doctors' time led to what, in my opinion, is the fundamental cause of the loss in prestige—namely, the failure of doctors, especially within the last five years, to afford patients a thorough, if perhaps old-fashioned, clinical examination, and in this way to merit their confidence. Let me hasten to say that there is a minority (I fear this is the word) of doctors who refused to be stampeded by numbers and still perform this obvious duty in the most commendable fashion.

The advent of the Danckwerts award has brought a satisfactory conclusion to the fight for adequate remuneration. Might I suggest that in return for this the general practitioner should undertake to send no patient to hospital without such examination as is possible with the equipment to hand in his consulting-room? I feel that this, more than the new College, would materially improve the stature of the doctor. It would be a real godsend to out-patient departments and hospitals generally, and could not fail ultimately to benefit the patient.—I am, etc.,

Belfast. S. T. IRWIN.

The Metric System

SIR,—I have been very much amused by the discussion on the pros and cons of the metric system. What strikes me is that most of the objections expressed by your correspondents are so very childish. I have never heard anybody asking for "nought comma nought nought nought five" of any drug (I quote Dr. R. A. C. Herron (*Journal*, April 25, p. 938). Like everybody else, I would ask for "half a milligram."

Decimals are no difficulty whatsoever. We prescribe two centigrams of morphine and one milligram of strychnine. I have never heard of anybody putting a comma in the wrong place and so sending his patient to a premature death.

First, when dealing with dangerous drugs we write the quantities in full—for example, morphine two centigrams—and *never* 0.02 g. But if we were to do it and misplace a comma the mistake would be so glaring that the chemist would be bound to notice it.

I understand the attitude of those who think the change-over would be difficult, but too many of your correspondents seem to take an impish pleasure in inventing possible difficulties which never arise in practice.—I am, etc.,

Messei, France. GABRIEL MOUCHOT.

Anticoagulants in Myocardial Infarction

SIR,—I would like to congratulate Dr. A. M. Cooke and his colleagues (*Journal*, April 25, p. 911) on their interesting and most practical paper on the use of anticoagulants in myocardial infarction. The problems related to the use of these drugs in this condition are of great importance to general practitioners, of whom I am one. These problems as I see them are as follows.

Should all cases of myocardial infarction receive anticoagulant therapy, or should strict selection be observed? If this selection is carried out, it should be on a practical and clinical basis. What, then, are the most accurate clinical points for selection? Should they be with respect to pain, its duration and severity, the degree of shock and its duration, or the age and sex of the patient, and should the previous history of angina be a major influencing factor? Having selected the case for anticoagulant therapy, where should this treatment be given? If in hospital, due consideration must be given to the practical questions of space and bed availability and the economic cost, as stressed in Dr. Cooke's paper. In 1951 there were almost 60,000 deaths from myocardial infarction in this country, a rate of 1.3 per 1,000 of the population. The average mortality rate quoted for this disease is around 30%, and, if this is accepted, then there must be some 200,000 new cases of this disease each year in Great Britain alone (a rate of almost 4 per 1,000). If only half of these are accepted for anticoagulant therapy and if, as is usually advised, this be given to in-patients, then 100,000 beds will be occupied for at least three weeks at a cost of £6m. a year. Anticoagulant therapy can be administered at home, provided that one understands its nature and dangers and that adequate and close co-operation exists between the general practitioner and the local pathological service for the estimation of the prothrombin time at frequent intervals. Unfortunately such pathological facilities exist in too few areas.

A third problem is whether hospital figures and reports depict the true natural history of the disease—for it may be that only the more serious cases are being reported and that the disease is in fact a much milder condition. I am a single-handed practitioner, and any figures that I quote will of course represent a mere drop in the ocean when compared with the hundreds and thousands of cases quoted by the experts. My few figures do, however, show that myocardial infarction seems to present, at least in my South-east London practice, a similar picture to that depicted in hospital reports. In my practice during the past three years (April, 1950, to March, 1953) there have occurred 44 new cases of proved (either by E.C.G. or necropsy) myocardial infarction. Of these 44 patients, 17 (40%) are now dead. Of these 17, 9 were sudden deaths who had received no previous treatment for the condition. The corrected mortality rate comparable with those who would have reached hospital is 23%, bearing in mind that none of my patients received any anticoagulant therapy. These mortality figures therefore are very similar to those quoted from hospital records, which vary from 50% to 15%.

My three main points, then, are that there is a need for some clarification of indications on the proper selection of cases of myocardial infarction for anticoagulant therapy; that this therapy could be managed in general practice, provided that adequate pathological facilities are open to general practitioners; and that the natural picture of the disease presents the same serious mortality levels in general practice as it does in hospital, and therefore special measures such as anticoagulants are indicated in order that this mortality rate be lowered.—I am, etc.,

Beckenham. JOHN FRY.

"A Happy Event"

SIR,—May I be allowed to underline your foresight and past contribution to progress in the controversy referred to in your leading article under the heading "A Happy Event" (*Journal*, April 11, p. 824)?

America, through Wells and Morton, had the greater share of the honour of the discovery of anaesthetics, but we fought the battle against the prejudice surrounding the use of anaesthesia, particularly in childbirth. My great-grand-uncle led this long and hard fight, and to him more than to any other must have come with satisfaction the news which meant that the issue was virtually decided. In a letter from his friend, Sir James Clark, dated April 19, 1853, he had the pleasure of reading "that the Queen had chloroform exhibited to her during her late confinement." The letter goes on: "It acted admirably. It was not at any time given so strongly as to render the Queen insensible, and an ounce of chloroform was scarcely consumed during the whole time. Her Majesty was greatly pleased with the effect," etc.

Simpson, by discovering the anaesthetic value of chloroform, did much to promote the whole method of anaesthesia, as Dr. Snow's work greatly improved the technique, but I sometimes wonder whether Simpson is sufficiently remembered as a pioneer of that humane standard of medical and surgical treatment which is characteristic of the present day and which we take absolutely for granted. There may be members of the profession, let alone the general public, who do not realize the revolution since the days, not so remote, when it was believed by many that suffering was good for the soul, and that the pains of childbirth were part of a divinely ordained order which should not be tampered with.—I am, etc.,

Halifax. IAN SIMPSON.

Treatment of Addison's Disease

SIR,—Although you mention some results of the supplementary use of cortisone in your annotation (*Journal*, April 18, p. 876), these comments appear to be detached from the sentence in which you record my speaking on the value of deoxycortone acetate at a recent meeting of the Royal Society of Medicine, in which I covered the therapeutic field. I should be obliged, therefore, if you would permit me to add that I reported that, of twenty patients treated for a number of years on deoxycortone, nine were alive and reasonably well with an average survival of seven years, nine were dead with an average survival of three years, and the fate of two was uncertain, hypoglycaemia being a common cause of sudden and unexpected death.

I recorded my experience with cortisone in physiological doses, which by itself can be more effective than D.C.A. (and is easily given by mouth), although some patients on cortisone require salt and D.C.A. in addition. I suggested that cortisone, where available, was particularly advisable for those patients on D.C.A. who were liable to hypoglycaemic phases, who lacked physical strength sufficient to do their daily task, who showed changes of personality such as apathy, negativism, and lack of enterprise, and/or whose electrocardiograms showed abnormality. All these things reverted to normal under cortisone therapy. Hitherto the use of cortisone in Addison's disease in this country has been limited by two considerations: (1) cost and availability, and (2) the knowledge that in animal experiments, and in some humans, large doses had appeared to produce a spread of a localized tuberculous lesion. As cortisone makes such a fundamental difference to the results of the treatment of Addison's disease, and as the quantities required are relatively small compared with those required for non-endocrine diseases, and as the total number of patients with Addison's disease is relatively small, it is hoped that the first difficulty will soon be overcome. As regards the danger of the spread of a local tuberculous lesion, I took the view that physiological or sub-physiological doses—for example, 25 mg. daily—were not likely to cause such a spread, and might even guard the patient against it, in so far as adrenalectomized animals were themselves hypersensitive to infection, and experience in America over a number of years in Thorn's clinic had not revealed any such misadventure.—I am, etc.,

London, W.1. S. LEONARD SIMPSON.

Vitamins

SIR,—When Dr. Audrey Z. Baker (*Journal*, April 25, p. 940) claims that we can now make estimates within relatively narrow limits of human daily needs of vitamins, I feel that she might have stressed the word "relatively." We can often estimate the amount of vitamin required to produce saturation in an individual, and indeed perform sundry other estimations with some exactitude. But I think she will agree that, until we can form an accurate estimate of the optimum as well as the minimum daily requirements, to say nothing of the extent to which, and the conditions under which, the body will manufacture its own vitamins, her assertion is a little enthusiastic. Even the Report of the B.M.A. Committee on Nutrition, 1950, to which she refers, admits that its figures are based on slender evidence (p. 16, para. 52).

Miss Stella Doraiswami and Professor J. Yudkin,[1] using one test for one vitamin at a time when rationing was still stringent, expressed their findings with true scientific caution. They mention that their findings were not confirmed in less stringently rationed subjects. In any case, if Miss Doraiswami and Professor Yudkin, or, indeed, any other competent investigators, discover that someone's diet is in some respect deficient, surely the right thing to do is to correct the diet, as Dr. W. W. Yellowlees (*Journal*, April 25, p. 939) points out—not to give daily pills.

Unlike Dr. Baker, I see nothing incongruous about awaiting some evidence of a condition before I agree that it is present. If, as the vitamin protagonists would have us believe, there is fairly widespread subclinical avitaminosis, one would reasonably expect a fair modicum of cases of overt primary avitaminosis to turn up from among them. In fact such cases are most rare and are found almost exclusively among persons who have been subsisting on weird or severely restricted diets. It would be interesting to see whether a controlled experiment on the lines of Professor Yudkin's would show any effect of a daily vitamin supplement with present-day rations. Such evidence as we have strongly suggests it would not. Therefore, while still admitting the value of vitamins in vitamin deficiency, I stick to the view which I

am interested to hear was held 20 years ago. I am interested to find also that vitamin research so far has done nothing to refute it. Having then stuck my neck out by asserting that a daily vitamin supplement is useless to the normal adult, I now extend it still further by defying Dr. Baker to produce evidence that this is not so. If she succeeds we must all advocate daily vitamins for the entire population.

Dr. E. V. Bevan (*Journal*, April 25, p. 939) is quite right. I use the commonly prescribed expectorants mainly as a placebo, and penicillin only when I consider I am dealing with an organism sensitive to it. If Dr. Bevan's experience teaches him otherwise, he will no doubt advocate a daily dose of penicillin and/or aureomycin for the Cambridge crew. He would be on stronger ground than he is with the vitamins.—I am, etc.,

London, W.9. A. LEWIS.

REFERENCE

1 *British Medical Journal*, 1948, 2, 708.

Stevens-Johnson Syndrome

SIR,—The case of Stevens-Johnson syndrome described by Dr. C. Romer (*Journal*, April 4, p. 768) seems to be a typical example of this condition, which, however, is not so rare as he supposes. It is certainly less common in children, but the full account given in your columns by Sneddon[1] includes the case of a boy of 9, whereas Klauder[2] described three such severe cases.

Dr. Romer's treatment was certainly energetic, but I feel that he is under an illusion in thinking that the patient's prompt improvement was entirely due to it. There is no specific treatment for erythema multiforme, which is a self-limiting condition, though salicylates, cortisone, and A.C.T.H. have a suppressing effect; of course it is right to deal vigorously with secondary infection.

I must quarrel with him, however, in criticizing the apparently long-winded dermatological names that are used—such as "erythema multiforme exudativum major" or "bullosum." When terms are used to describe particular conditions they are surely meant to help us to understand what we are regarding, and heaven knows we understand little enough. Dermatologists realize that erythema multiforme is not a specific disease but merely a morphological skin reaction which may result from many different causes (herpes simplex, streptococcal infections, tuberculin injections, and drugs are but a few examples of various initiating factors). Erythema multiforme may furthermore be "minor," moderate, or "major" when the mucocutaneous junctions are severely affected. Are we not nowadays trying to drop the use of these various eponyms when aetiology is neither uniform nor proven? For that matter Fiessinger and Rendu[3] described this same condition a few years earlier than Stevens and Johnson, but unfortunately they did it in French and many are not aware of it.

Finally, Dr. Romer says that sulphonamides are unlikely to be a cause of this condition. I have little doubt that they occasionally may be responsible, and can record that I have seen three cases in the past six months which were due to barbiturate sensitivity.

If we regard erythema multiforme as more like urticaria than cretinism, mongolism, or pink disease, we shall be able to appreciate better the many different factors which may precipitate it.—I am, etc.,

London, W.1. STEPHEN GOLD.

REFERENCES

1 *British Medical Journal*, 1947, 1, 925.
2 *Arch. Derm. Syph. (Chicago)*, 1937, 36, 1067.
3 *Paris méd.*, 1917, 23, 54.

Polypharmacy

SIR,—Dr. A. T. Mennie (*Journal*, April 18, p. 887) seems to think that most of the anaemic people in Britain to-day are anaemic from malnutrition, and that nutritional megaloblastic anaemia is common. Both these beliefs are wrong. In Britain to-day iron-deficiency anaemia is usually caused by pregnancy or by pathological bleeding, not by malnutrition. Most iron-deficient patients who fail to respond to iron salts by mouth respond quite well to intravenous saccharated iron hydroxide; but they do not respond to liver or to folic acid. Slight differences in the speed of response to treatment are of little practical importance, because oral therapy with iron should be continued for some weeks after apparent cure, and the dosage of intravenous iron is determined by the initial haemoglobin level and the body weight.

Nutritional megaloblastic anaemias are very rare. I have never seen that of pellagra nor that of infancy, and but five cases of megaloblastic anaemia of pregnancy among over 13,000 pregnant women. In Britain our common megaloblastic anaemia is pernicious anaemia, which is not a nutritional anaemia. Pernicious anaemia is better controlled by vitamin B_{12} than by liver (Asher, R., and Brewerton, D. A.[1]). It is well known that folic acid may precipitate subacute combined degeneration of the cord in a previously untreated patient suffering from pernicious anaemia. Sub-optimal treatment of pernicious anaemia produces peculiar non-specific blood and bone-marrow changes which make diagnosis difficult or impossible. Can Dr. Mennie wonder if I maintain that the remedy under discussion is unnecessary and probably dangerous, and that its introduction was against the best interests both of the patient and of the country?—I am, etc.,

London, N.W.10. GEORGE DISCOMBE.

REFERENCES

1 *Lancet*, 1952, 2, 265.

Mental Hospital Service

SIR,—On re-reading our letter (*Journal*, March 7, p. 560) we must agree that—taken literally—Dr. Otho FitzGerald's challenge (*Journal*, April 4, p. 781) regarding occupational therapy for chronic patients appears to be justified. Nothing, however, was further from our minds than that chronic patients need no occupational therapy. The point we sought to make was that with the available medical staffs in most mental hospitals to-day it is impossible for both acute and chronic patients to receive adequate treatment. Since a choice between the two has to be made, it is better from a long-term point of view for the doctors who are available to spend their energies on doing everything to get recently admitted patients out of hospital and thereby in time reducing the number of chronic patients.

With regard, however, to Dr. FitzGerald's later suggestion in his letter, that we seem to be uninterested in the incurable patients, we feel that our letter does not suggest this, nor is it in fact true in any way. What is true is that, as a result of modern treatments, many patients who in former years remained in the hospitals as good chronic workers are now discharged, so that the "quality" of the chronic hospital population is steadily deteriorating and the number of workers becomes lamentably small. Until we can cure *all* our patients, we believe it is better to intensify this state of affairs rather than devote so much time to our chronic patients that we are unable to do everything possible for the acute patients. The ideal solution is to have enough medical staff to cope with acute and chronic patients—but where can we find such staff, and who would pay them if we could find them?

Lastly, a word as to our own practice. We have both "graduated" in hospitals where the standard of care for chronic patients was of a high order. At the risk of once again giving a false impression we must insist that as things stand at present the number of patients who have been in hospital for more than five years and who recover is comparatively small, and that the more efficiently the patients have been treated in the first place the smaller this percentage of recoveries becomes. It would therefore be better to regard occupational therapy for chronic patients as a means of preventing mental deterioration, and this conception in no way diminishes the importance of what we can do for the chronic patient. Our real contention is that, with social services different both in quality and quantity from those existing in most hospitals to-day, much more could be done towards getting chronic patients out of hospital into sheltered social and working environments.—We are, etc.,

R. A. SANDISON.
A. M. SPENCER.

Worcester.

POINTS FROM LETTERS

Prophylaxis of Tetanus

Dr. T. DAVID LAMBERT (Ruislip, Middlesex) writes: I note with interest the letters by Drs. A. H. Morley (*Journal*, March 28, p. 730) and K. M. Hay (p. 733) regarding prophylaxis of tetanus. During the past five years I have had two cases of tetanus in my practice, both in children and one fatal. This prompted me to suggest to a well-known firm that it was high time that there was made available a combined diphtheria-pertussis-tetanus toxoid to be given from the age of 7 to 8 months, and to be followed by a boosting dose later. I understand from the firm in question that this toxoid is now ready for its trials, and I hope that if it proves successful the idea will be taken up in enthusiastic fashion. I am sure that it will be of benefit both to patient and to doctor.

Chickenpox

Dr. M. D. WARREN (London, W.5) writes: I was most interested to read Dr. James A. Petrie's letter (*Journal*, April 11, p. 836). Last April I had the misfortune to catch chickenpox from one of my children, and the day before the eruption appeared I had had an appointment with my dental surgeon. The eruption, although ultimately covering the body, was particularly dense and occurred early on the buccal mucosa on the side where the dental surgeon had been manipulating. It might also be of interest to record that during the attack I scratched certain lesions and not others. When the eruption had faded I could find no evidence of correlation between scratching and scarring; a few lesions of both the scratched and unscratched groups have scarred. I have also seen a case of chickenpox with the greatest number of lesions in the area of a burn sustained during the incubation period. The aggregation of lesions in an area of trauma is a well-known feature of smallpox, and the relationship of trauma and paralysis in poliomyelitis has been widely noted. All these conditions are virus infections, and perhaps the explanation lies in the fact that the virus is better able to establish itself in a fatigued or damaged cell than in a normal one.

Chlorophyll as a Deodorant

Dr. WM. MITCHELL (Chief Chemist, the Allen Chlorophyll Co., Ltd., London, N.1) writes: I think two conclusions can be drawn from Professor Stanley Alstead's asparagus experiments (*Journal*, April 11, p. 832): (*a*) that he and his colleagues are peculiar in failing to respond, or (*b*) that, despite earlier claims, chlorophyllin is ineffective for this purpose. But, even if conclusion (*b*) is correct, that in itself would by no means prove that chlorophyllin has no therapeutic or deodorizing properties in man. I have already said that I think systemic action, thereby implying absorption from the gastro-intestinal tract, is unlikely. But is the alimentary canal not itself a likely "site of action"? I commend the critics to ponder on the fact that chlorophyllins evidently accelerate the oxidation of mercapto groups to disulphides, and also on the role that glutathione and associated substances are believed to play in oxidation-reduction processes in the body by virtue of the reversible mercaptan-disulphide mechanism. The two things may not be unrelated. Pending much more chemical, biochemical, and clinical work it would seem more reasonable to defer judgment rather than to rush in on the basis of a few scrappy experiments (or even no knowledge at all) and dismiss the matter. In the present state of our knowledge, or rather lack of knowledge, of drug action the critics appear to be rash, to say the least.

Television and the Patient

Dr. ELIZABETH M. R. GARRIGAN (Talgarth, Brecon) writes: Unlike Dr. Trevor Hughes (*Journal*, April 18, p. 884), I saw the television broadcast of "Matters of Medicine—Pain." I doubt whether this particular presentation, excellent though it was, served to do what it set out to—namely, educate the layman. The level of the broadcast, in my opinion, was too advanced and detailed to be helpful to the general public, and I feared more harm than good would result. The medium of television can be a powerful factor in educating all in matters of medicine, but let us show a sense of balance in its use.

Lumbar Puncture

Dr. WILLIAM EDGE (Salford) writes: In the recent article on lumbar puncture it was stated that the patient has to be on his left side. I have met with this statement before, but see no reason why the patient cannot be on his right side. In fact, I have done it with the patient on either side without any noticeable difference. A patient recently has had 90 lumbar punctures (for tuberculous meningitis), all while lying on her right side, and, what is more, she has made a complete recovery.

Obituary

Sir ROBERT G. ARCHIBALD, C.M.G. D.S.O., M.D.

Sir Robert Archibald, professor of bacteriology and parasitology in Farouk University, Alexandria, died suddenly at the age of 72 on May 2, while on a visit to Salisbury, Southern Rhodesia. Most of his career as a medical research worker and teacher was spent in the Sudan and in Egypt.

Robert George Archibald was born in India on July 4, 1880, the son of the Reverend W. F. Archibald, a Presbyterian chaplain to the Forces. From Dollar Academy he went on to study medicine at the University of Edinburgh, where he graduated M.B., Ch.B. in 1902. For three years he was in the university's cricket team. After holding a number of resident hospital appointments—at the Northern Hospital, Liverpool, St. Mary's Hospital for Women and Children, Plaistow, and the County Asylum, Rainhill—he joined the R.A.M.C. in 1906, winning the prize in pathology at the Army Medical College, Millbank, in that year. Soon after being sent out to Egypt he was seconded to the commission of inquiry into sleeping sickness in Uganda, led by David Bruce. On his return to Egypt Archibald was attached to the Egyptian Army, seeing service during the Blue Nile operations in 1908, and being mentioned in dispatches. During the first world war he served with the Mediterranean Expeditionary Force at the Dardanelles, again being mentioned in dispatches, and later went with the Darfur Expedition into the Sudan, being awarded the D.S.O. in 1917. Having proceeded to the degree of M.D. in 1918, he retired from the Army in the following year and was appointed director of the Wellcome Tropical Research Laboratories, Khartum. In 1928 he became director of the Stack Medical Research Laboratories, also at Khartum. Appointed C.M.G. in 1928, Archibald was knighted in 1934, retiring from his work in the Sudan two years later.

After leaving Africa Archibald went to the West Indies, becoming medical superintendent of the Chacachacare leper settlement in Trinidad, and at the beginning of the second world war he returned to this country to live at Canford Cliffs, Dorset. Being quite incapable of remaining idle, he was soon immersed in the development of the laboratory service in Dorset, being appointed director of the branch county laboratory at Poole, where he was also a consultant in tropical diseases. His ability for organization also proved useful in civil defence, and he was group controller of the casualty services in the Poole, Bournemouth, and Christchurch area. Advancing years failed to take the edge off his keenness to undertake work of responsibility, and in 1947 he returned to Egypt as professor of bacteriology in the Farouk University, Alexandria, becoming also professor of parasitology in 1949.

Archibald had good looks, a fine physique, worldly wisdom, and a benevolent outlook on life. He was inspired by a faith which made work for others, especially the Sudanese, the guiding impulse of his life. Perhaps it also made him a little restless. His kindness was proverbial, and he was of course a popular man, to whom people turned for advice on their personal and professional problems. However busy, he had a welcome for everyone and a sincere desire to help them.

In 1919 he married Olive Chapman, only child of Arthur Cant, of Colchester. There were two daughters of the marriage.

We are indebted to Dr. D. RIDING for the following appreciation: In writing about "Archie," as Sir Robert Archibald was known to his friends, I cannot just say that he was a good and successful doctor respected and admired by all who knew him, for he was all that and more. His was a rare yet very human personality, which inspired men to follow him and caused all to love him. Born and brought up among folk who equated human progress with social, economic, moral, and spiritual advancement, he dedicated his life to the service of humanity. Even the bitter experience of the Gallipoli campaign failed to shake his faith in mankind and his belief that good must inevitably triumph over evil.

A worthy successor to Chalmers and Andrew Balfour as director of the Wellcome Tropical Research Laboratories, Archibald threw all the energy of which his magnificent physique and active brain were capable into that great experiment—the opening up of the Anglo-Egyptian Sudan. His tall, athletic figure, polo helmet, major's cane, and white bull-terrier will long be remembered by the older generation of his beloved Sudanese. In spite of long hours spent in pioneer investigations into sleeping sickness, bilharziasis, and the diseases of the cotton plant, Archibald always found time for the practice of medicine, and no man, woman, or child—black, brown, or white—ever asked for his help in vain.

Whatever Archie did he did well. He was a fine rugger player, a good dancer, an excellent after-dinner speaker, and a skilful fisherman when he sought the sea-trout in the River Esk at Langholm.

There is a saying that they that drink of the waters of the Nile will return. Perhaps, when the dark clouds looming over Africa have dispersed, the spirit which Archibald represented will return, and other young men will go out from Scotland—the homeland of Archibald, Andrew Balfour, and Livingstone—to the far places of the world to prove that Robert Burns was right when he wrote:

> "It's coming yet, for a' that
> That man to man the world o'er
> Shall brothers be for a' that."

Professor ROBERT KIRK writes from University College, Khartum: When Archibald was attached to the Egyptian Army in 1908 he was appointed assistant pathologist and bacteriologist in the Wellcome Tropical Research Laboratories, Khartum, which was then a department of the Gordon Memorial College. Here he was destined to spend the next 28 years (save during the 1914–18 war), years of memorable service during which the Wellcome Laboratories in Khartum became world famous as an institute of tropical research under the direction of Sir Andrew Balfour, of Dr. A. J. Chalmers, and finally of Sir Robert Archibald himself. When he retired the laboratories were divided among various departments of the Sudan Government. Archibald's service in the Sudan was a time of intense productive activity. He contributed numerous papers to the famous *Reports of the Wellcome Tropical Research Laboratories*. With Balfour he compiled the *Reviews of Recent Advances in Tropical Medicine*, published as supplements to the *Reports* and subsequently continued as the *Tropical Diseases Bulletin* by the Bureau of Hygiene and Tropical Medicine in London. He was a contributor to the *Oxford Index of Therapeutics* (1921) and editor (with Dr. W. Byam) of the monumental treatise in three volumes entitled *The Practice of Medicine in the Tropics*. Archibald's own researches during this period are scattered through the scientific and medical journals in innumerable articles covering almost every aspect of tropical medicine and hygiene. He was local secretary of the Royal Society of Tropical Medicine and Hygiene, president of the Sudan Branch of the British Medical Association, member of the executive committee of the British Empire Leprosy Relief Association, and a corresponding member of the Société de Pathologie Exotique. He was one of the original members of the council of the Kitchener School of Medicine, and later a member of the executive committee in London. He was also a member of the executive committee of the University College of Khartum. Although it is nearly twenty years since Sir Robert Archibald left the Sudan he is still remembered there with deepest affection and respect—the good physician, able investigator, wise administrator, kind teacher, and great gentleman, whose death symbolizes the passing of an era.

ALEXANDER MILES, M.D., LL.D., F.R.C.S.Ed.

Mr. W. J. STUART and Mr. JAMES M. GRAHAM write:

We feel it to be a duty to refer to the appreciation of Mr. Alexander Miles by Dr. Harley Williams in the *Journal* of April 25 (p. 942). We have no wish to detract from his praise of Mr. Miles; the main part of the obituary notice by one of us (W. J. S.) is evidence of his admiration and respect for Mr. Miles. But Dr. Harley Williams, quite unintentionally we are sure, has been led away by an antithesis, and is so unfair to Alexis Thomson that we feel bound to defend his memory. One of us (W. J. S.) was assistant surgeon to Alexis Thomson in hospital from 1903 to 1909, assisting him at every operation; while the other (J. M. G.) was his university assistant for 14 years and his private assistant for a similar period. We therefore had an exceptional opportunity of knowing Alexis Thomson as a man and as a surgeon.

Dr. Harley Williams describes Alexis Thomson as "brilliant, eccentric, reckless." He was quite exceptionally brilliant—breezy in manner—but never in any way eccentric. He was a rapid and daring operator, but to call him "reckless" is a complete mistake. Dr. Harley Williams, speaking of Thomson and Miles, says, "Each was everything that the other was not." Miles was "cautious, careful, conscientious . . . the conscientious partner in that team." It is most unfair to refer to Alexis Thomson as the opposite of that description. Then at the final examination Thomson is described as "impetuous, impatient, and then bored," and Miles "ran the show, calmed the alarmed examinee, and supplied the proper efficiency and fairness." We have both examined with Alexis Thomson over many years, and this is simply not true. We believe that Dr. Harley Williams did not intend to write in derogatory terms regarding Alexis Thomson, but, if he will re-read his appreciation of Mr. Miles, we are sure that he will understand how much pain it has caused to surviving colleagues and relations of Alexis Thomson, and why we have felt compelled to write this note.

W. T. LONGCOPE, M.D.

Dr. Warfield Theobald Longcope, emeritus professor of medicine at Johns Hopkins University, Baltimore, died at his farm near Lee, Massachusetts, on April 25, aged 76. He had the great good fortune of a medical education at Johns Hopkins when Welch, Osler, Halsted, and Kelly were among his teachers. After graduating in 1901 he was appointed resident pathologist at the Pennsylvania Hospital, Philadelphia, and three years later he was made director of the Ayer Clinical Laboratory. From 1909–11 he was associate professor of applied medicine at the University of Pennsylvania. Longcope then moved to New York, and from 1914–21 occupied the Bard chair of applied medicine at Columbia University. During this period he was associated with the Presbyterian Hospital, and became physician-in-chief there. In the first world war he served in France as a colonel in the Medical Corps of the Ameri-

can Expeditionary Force. In 1922 he returned to Johns Hopkins University to take the chair of medicine, at the same time being appointed physician-in-chief at Johns Hopkins Hospital. He retired from these posts in 1946. Longcope was an excellent organizer who initiated and carried through a mass of experimental and clinical work, principally on the pathology of the lymphatic and haemopoietic systems, but he also investigated pneumococcal infections, paratyphoid fever, cardiac hypertrophy, aortic insufficiency, and serum sickness. The chapter on Hodgkin's disease in Osler's *Modern Medicine* (1909) was contributed by him. Longcope had a background of culture and erudition which, despite his reserve, particularly fitted him for the chair at Johns Hopkins.

Sir JOHN MCNEE writes: With the death of Warfield Theobald Longcope the second generation of clinical teachers at Johns Hopkins who followed the famous "big four" in Sargent's picture—Osler, Halsted, Welch, and Kelly—is about at an end. Actually Longcope did not succeed Osler—there was an interval when Thayer and Lewellys Barker in turn occupied the chair—but Longcope became the first "whole-time" professor of medicine, and remained for 24 years. I cannot be dogmatic, but I think that Longcope was the first, or very nearly the first, professor of a clinical subject in America who was "whole-time" and confined his clinical work entirely to within the hospital. It was during his service in France in the first world war, and later when he was in Baltimore, that Longcope became so well known to many British physicians. His personality endeared him to all his students and all his friends. He was upright, unselfish, modest, and interested in many things beyond medicine—a perfect gentleman and a greatly loved teacher. His last years were clouded by chronic illness, and when I last stayed with him in 1949 his emphysema was obviously causing him much distress. He still worked on, however, giving occasional lectures to medical societies, attending medical meetings, writing to and discussing problems with his old students and friends, and making ward rounds with the physicians at Lee Hospital. He held the affection and esteem of all American physicians, and was awarded all the distinctions which were his due, including the presidency of the Association of American Physicians. Longcope had many good friends in Britain, and they will be sorry to hear of his death. The younger generation of physicians are certain to remember some of his well-known contributions to clinical research.

We record with regret the death of Dr. H. J. M. BROWNE at Hoylake, Cheshire, on March 16, at the age of 84. Hablot John Moxon Browne was born on February 6, 1869, the eldest son of the late Mr. Edgar Browne, an oculist of Liverpool, who took a leading part in the building of the Eye and Ear Infirmary in Myrtle Street, Liverpool (now the Liverpool Ear, Nose, and Throat Infirmary), and the grandson of Hablot Knight Browne, better known as "Phiz," the illustrator of books by Charles Dickens. He was educated at Berkhamsted School and at the University of Edinburgh, graduating M.B., C.M. in 1892, and proceeding to the M.D. in 1907. He then spent a year at the University of Bonn, and later became house-surgeon at the Liverpool Royal Infirmary and at the Birkenhead and Wirral Children's Hospital. Thereafter, for nearly half a century he practised in Hoylake, where for many years he was medical officer to the Hoylake children's day nursery, being all his life specially interested in paediatrics. We are indebted to Dr. J. A. ELLIOT for the following appreciation: Hablot Browne was a delightful example of a type of general practitioner that must be nearly extinct now. He was unhurried, courteous, calm, wise, tolerant, and amusing. Widely read in general literature as well as medical, he was up to date in the latter to an amazing degree. I shall always remember him as a good friend, companion, and colleague. In his parents' home he met many well-known people, and I have often heard him talk of Ellen Terry, Henry Irving, and of the famous comedian John Toole, who was sometimes even more amusing in private conversation than he was on the stage. Dr. Browne possessed a number of interesting relics of "Phiz," including several original drawings of the Pickwick series, and many of the paper-covered fortnightly parts in which *Pickwick* appeared. He was married three times and leaves a widow and a son.

We record with regret the death of Mr. PATRICK KINMONT at Chesterfield on April 3 at the age of 76. Born on June 27, 1876, Patrick Kinmont studied medicine at the University of Edinburgh, where he graduated M.B., Ch.B. in 1897, proceeding to the M.D. in 1908. He was elected F.R.C.S.Ed. in 1901. After graduation he held house appointments at the City and County Royal Infirmary, Perth, and at Dundee Royal Infirmary, and then volunteered for service in the war in South Africa as a civil surgeon with the South African Field Force. On his return to England he was senior house-surgeon at the Lincoln County Hospital until 1904, when he settled in practice at Newark-on-Trent, becoming surgeon to the Newark Hospital. In 1905 he married Miss Marie Clifford, who was a sister at the Lincoln County Hospital. Mr. Kinmont, who was loved and trusted by all his patients, quickly developed a large and busy practice, general and surgical. He was a J.P. for Newark. During the first world war he served with the R.A.M.C. and was surgical specialist to the 21st Stationary Hospital, Middle East Force. In the last war he was in charge of the first-aid services at Newark. In 1939 he was invited to be president of the Nottingham Chirurgical Society. His wife died in 1942, and although he continued his work in Newark until 1946 he never recovered from his great loss. Mr. Kinmont founded the Newark Caledonian Society and was its president until the day of his death. An eloquent Scot, he was much in demand all over the country on occasions, such as a "Burns Night," when his talents were specially appreciated. In his spare time he enjoyed fishing, shooting, and golf. He is survived by a son, Dr. P. D. C. Kinmont, and three daughters, to whom our sympathy is extended.—N. E. K.

Dr. JOYCE MITCHELL, who was well known to practitioners in the Bromley area of Kent, died at her home in Bromley on April 14. Joyce Clementine Blackwood Mitchell studied medicine at Edinburgh University, where she showed unusual gifts as a student, and was awarded the Dorothy Gilfillan Memorial Prize in 1918, the year she graduated. When her husband, Mr. J. Ewart Purves, was appointed the first surgical specialist to the Lewis Hospital in the Outer Hebrides, Dr. Mitchell accompanied him and lived in Stornoway for many years, holding for a time the appointment of honorary pathologist for the Isle of Lewis. She had a keen analytical mind with an affectionate and sensitive temperament, possessing intuitive perception into people's troubles. She observed, and suffered, more than most human beings, yet there was in her an essential buoyancy and charm which vanquished the harsh realities of life. Besides undertaking pathological work she assisted her husband with anaesthetics, and her fresh ideas and warm understanding were greatly prized by her circle of friends. When her husband moved to Bromley Dr. Mitchell became the conscientious secretary of the Bromley Division of the B.M.A., faithfully attending all meetings, and taking an interest in local causes such as the Y.W.C.A. Joyce Mitchell belonged to what might be called the second generation of women doctors—those who came after the early pioneers and whose professional vocation, though accepted, had not become entirely customary. She was a champion of some causes which at one time seemed unconventional but later were fully realized. Deep sympathy will be felt for Mr. Ewart Purves and their only daughter, Dr. Rosabelle Purves, who is specializing in obstetrics.—J. H. H. W. and H. J. P.

Medical Notes in Parliament

N.H.S. Costs Inquiry

Mr. SOMERVILLE HASTINGS asked the Minister of Health on May 7 what knowledge and experience of the work and management of hospitals was possessed by the members of the Committee that was to inquire into the cost of the Health Service.

Mr. IAIN MACLEOD pointed out that he had told the House that the inquiry was to be independent and objective. The members, therefore, had no direct connexion with any part of the Health Service. The Committee would decide their own procedure, but he had no doubt that they would wish to take evidence from organizations and individuals with knowledge and experience of the working of the Service.

Mr. HASTINGS asked if the Minister did not feel that some knowledge of the work of a hospital was necessary for those whose job was to assess the value of what was spent on the hospital. Mr. MACLEOD disagreed. If once they started having "representatives" of hospitals, in any sense of the term, there would have to be representatives of doctors, dentists, consultants, local authorities, opticians, and the rest. He wanted the problem to be examined by a committee of five wise men—or four wise men and a wise woman—and he thought they would get the best result from that.

Costs and Charges

Major TUFTON BEAMISH on May 6 asked the Minister of Health what extra cost would fall on the Exchequer in this financial year if the National Health Service were made free in all respects.

Mr. IAIN MACLEOD pointed out that it was difficult to estimate the level of demand that would result if charges were removed, and therefore no accurate estimate was possible, but he thought that the extra cost in a full year would be at least £40m.

Merit Awards

Dr. SANTO JEGER asked the Minister of Health on May 7 how the recipients of merit awards were chosen among specialists under the National Health Service Act; and how many awards had been made each year since the system was instituted.

Mr. IAIN MACLEOD explained that the awards were made on the recommendations of an advisory committee. 1,740 awards were made in England and Wales for 1948–9, 439 new or higher ones for 1950, and 229 for 1951. Recommendations had not yet been received for 1952. He added that the advisory committee had a professional chairman (Lord Moran) and a lay vice-chairman. There were representatives on it of the Medical Research Council, the universities, the Royal Colleges, and the Scottish Royal Corporations. Mr. SOMERVILLE HASTINGS asked if the same committee dealt with all the branches of consultants. Mr. MACLEOD said that it did, but it could of course take advice as it wished within its terms of reference.

Shortage of Junior House Officers

Dr. BARNET STROSS asked the Minister of Health on May 7 whether he was aware of the difficulty experienced by some hospitals in obtaining candidates for junior house positions; what was the extent of this problem; and whether he would consider increasing the payment for locums for these positions from the present rate of £8 per week.

Mr. IAIN MACLEOD said that this problem was widespread, particularly in the remoter hospitals. He was considering how it could be solved, but he did not think a solution could be found on the lines suggested.

Fog Inquiry

On May 7 Miss PAT HORNSBY-SMITH stated in answer to Dr. Santo Jeger that there was insufficient evidence to incriminate particular components of London fog as the contributory causes of death last December, but investigations were continuing.

On May 8 Mr. MARPLES, Parliamentary Secretary, Ministry of Housing and Local Government, replying to a short adjournment debate initiated by Mr. Dodds on much the same subject, said the Government had decided to appoint a committee of inquiry into the causes and effects of air pollution and to consider what further preventive measures were practicable. The personnel and terms of reference would be announced soon.

Fibre-glass and Lung Tissues

Mr. ELLIS SMITH on May 7 asked the Minister of Labour what action he was taking to minimize the injurious effects of fibre-glass in the aircraft and engineering industries, and if he would publish a full report after the factory inspectors had investigated the use of fibre-glass and similar new materials.

Sir WALTER MONCKTON replied that the factory department had maintained a close watch on the manufacture and handling of this material, but there was no evidence to show that it was injurious to the lungs, although it might give rise to mild skin irritation which soon disappeared. Samples of materials consisting of fibre-glass and resins used in the aeroplane industry were being investigated microscopically to determine the size and nature of the dust given off when components made from these materials were machined.

Mr. ELLIS SMITH said that the workers were concerned at the danger of a new wave of pneumoconiosis developing unless resolute action was taken. Dr. BARNET STROSS said that if fibre-glass and resin compounds were machined they were almost certain to give off microscopic particles that were bound to be injurious to lung tissues. Was there not, therefore, a prima facie case for great care? Mr. SOMERVILLE HASTINGS said the symptoms of pneumoconiosis took a long time to develop in many cases, and that it was many years before the disease became evident as a result of exposure to infection. Sir WALTER MONCKTON promised to give the matter his personal attention, but said he would rather wait for the report on the samples that had been submitted before he said any more.

Tuberculous Immigrants

Mr. IAIN MACLEOD, replying to Mr. Storey on May 7, said that the returns from medical officers of health made no distinction in nationality, so information about the proportion of tuberculosis notifications that referred to persons who had recently entered the country from Eire was not available.

Mr. STOREY said that the incidence of tuberculosis was 50% higher in Eire than in this country, and in some areas here a large proportion of infections were among people who had recently come from Eire. In view of that, would it not be a good thing to insist on radiographical screening and a certificate of fitness before allowing people from Eire to seek employment in this country? Mr. MACLEOD said there were a number of other people and Ministries involved in this. It was quite right that a certain amount of difficulty had been caused by people coming from Eire, and he would see whether more information ought to be obtained and whether action should be taken at the ports.

Pharmacy Bill

When the Pharmacy Bill was given a second reading in the House of Lords on May 5, Lord HADEN-GUEST mentioned that its intention was to prepare for the consolidation of the series of Acts that had gone before. The statutory duties of the Pharmaceutical Society would be put into the Bill, and the constitution of the Society into a new charter now before the Privy Council.

Lord AMULREE, who moved the second reading, said the Bill had the support of the Government and of the Pharmaceutical Society. Lord SHEPHERD gave it the blessing of the Opposition; and Viscount SAMUEL, recalling that he

was responsible, as Under-Secretary at the Home Office, for the passing of the Poisons and Pharmacy Act, 1908—then a highly controversial measure—said he entirely concurred in the amendment of that Act which was to be effected by the Bill.

Medico-Legal

DOCTOR LOSES LIBEL ACTION

[FROM OUR MEDICO-LEGAL CORRESPONDENT]

Dr. David Stark Murray, of Richmond, had judgment entered against him on May 7, 1953,[1] in an action for libel which he had brought against Associated Newspapers, Ltd., the printers and publishers of the *Evening News*. On February 12, 1951, there was published in "Talk of the Day" in the *Evening News* the following article:

"STARK FACTS

"Dr. D. Stark Murray—the Socialist doctor who, defending the Government's meat policy, said, 'Medically speaking, meat is not essential to health'—has another claim to fame.

"As a member of the South-west Regional Board and as a leading figure in the Socialist Medical Association he is chief protagonist in the attempt to turn out the 'rebel' doctors from the Kingston Victoria Hospital.

"NOT SO BITTER

"Indeed, some observers believe that the struggle, but for Dr. Stark Murray, might not have been so bitter or so uncompromising on either side. Rightly or wrongly, the Kingston Victoria Hospital doctors feel particularly strongly about Dr. Stark Murray. They claim that it was the Kingston Victoria Hospital which before the war gave him his first start in the district by letting him have a pathological laboratory there."

Dr. Stark Murray complained that the article was a grave imputation on him as a doctor, as a man, and as a member of the South-west Metropolitan Regional Hospital Board. It suggested that in the Kingston Victoria Hospital disputes he had assumed the role of champion in turning out the "rebel" doctors, and had used his position on the board and as president of the Socialist Medical Association to bring about a result he desired not on the merits but as a politician, and that he was wanting in gratitude and bit the hand that fed him.

The defence was that the words complained of were not defamatory or alternatively were true.

Dr. Stark Murray said in evidence that he had approached the problem of change of use of the Kingston Victoria Hospital purely as a member of the medical review committee of the board. There was neither place nor possibility of introducing political considerations, even if they had been applicable to the situation. He did not lay any claim to fame to turn the rebel doctors out of the hospital. He was not concerned in any way to injure any doctor, and had remained throughout on the best of terms with those with whom he had come into contact.

Cross-examined, Dr. Stark Murray was asked if he had publicly used words to the effect that the real grievance of the Kingston general practitioners in opposing the scheme was because they wanted to retain the hospital to make money out of the sick. He replied that he had not said that of all the doctors. The remark was well understood inside the medical profession, and was not likely to engender the bitterness suggested by the defence.

Brigadier Norman Skentelbery, of South Croydon, who for four years before May, 1951, had been chairman of the Victoria Hospital, said in evidence that a letter from Dr. Stark Murray to a Surrey newspaper published on December 2, 1950, was bitterly resented by the doctors at the hospital.

In his summing-up Mr. Justice Devlin told the jury that in considering whether the article was defamatory they must look at it as a whole to see whether substantially it could lower the plaintiff's credit and reputation in the eyes of the right-thinking world. The evidence was that when the opposition to the scheme manifested itself it was the plaintiff who first introduced politics into the matter. It had been said that the article imputed that the plaintiff was using his position on the board for political purposes. The defence had not suggested that the imputation was true. If the jury thought that the article as a whole bore that meaning it was a serious thing to say about a man in Dr. Stark Murray's position. None of the witnesses had suggested that the article had conveyed that meaning to them.

The jury returned a verdict for the defendants, and judgment was entered accordingly.

[1] *The Times*, May 8, 1953.

Universities and Colleges

ROYAL COLLEGE OF PHYSICIANS OF LONDON

At a quarterly comitia of the College held on April 30 the following, having satisfied the Censors' Board, were elected Members of the College: J. M. Bishop, M.B.; B. Bronte-Stewart, M.D.; L. J. Clein, M.B.; T. B. Counihan, M.B.; A. Cumin, M.B.; R. B. Goudie, M.B.; R. E. Gruchy, M.B.; P. F. Hall, M.B.; R. E. D. Harvey-Samuel, M.B.; P. M. Higgins, M.B.; R. Hoffenberg, M.B.; R. A. Hunter, M.D.; C. S. Livingstone, M.B.; Suzette M. Mettrick, M.B.; I. H. Mills, M.B.; M. A. Pears, M.D.; A. Polak, M.B.; A. T. Richardson, M.B.; Jean K. Ritchie, B.M.; J. H. Ross, M.B.; Irene P. Rowlands, L.R.C.P.; J. R. Seale, M.B.; B. Senior, M.B.; J. D. Sheward, M.B.; P. B. Stewart, M.B.; W. K. Stewart, M.B.; B. Strickland, M.B.; R. S. Thanabalasundrum, M.B.; J. P. D. Thomas, M.B.; J. I. Wand-Tetley, M.B.; E. K. Westlake, M.B.; W. D. Wilkey, M.D.; D. P. Winstanley, B.M.; A. R. H. Worssam, M.B.

Licences to practise were conferred upon the following 136 candidates (including 40 women), who have passed the final examination in Medicine, Surgery, and Midwifery of the Conjoint Board, and who have complied with the necessary by-laws:

R. G. Attenborough, Bridget K. Attlee, N. J. Badham, Patricia M. Banks, A. F. Barrett, B. A. J. Barrow, A. R. Bearn, J. S. Bennett, E. P. C. Benson, P. W. S. Blake, J. S. Bland, Evelyn A. M. Boesen, P. D. Bowen, J. J. Bradley, Cynthia I. Breillat, R. C. Brookes, Jennifer T. Bryant, E. A. C. Buckell, Katharine M. Cadbury, Ailleen M. Caldwell, Elizabeth O. Castell, P. S. N. Chappell, Ah Kwan Chia, Gillian M. Churcher, R. Clark, D. B. Clarke, Mary Clothier, J. Cocker, A. D. Cole, Barbara P. Coppen, D. C. Cornish, I. J. Cunningham, J. C. B. Daman, R. Danbury, Shirley F. Dauncey, Diana M. Dean, R. A. S. Dunn, J. V. Dyer, K. B. Edwards, W. K. Eltringham, R. W. Emmerson, G. Evans, A. Fletcher, W. Foster, D. B. Fox, R. C. Francis, P. W. Franks, A. C. Fraser, Gilliam M. Gandy, D. C. Gardner, R. E. M. Geldart, M. W. Gott, B. G. Gradwell, J. L. G. Griffiths, Hanna Grodzicka, J. A. Gumbrell, J. Ll. Harrington, G. G. Hill, P. O. Hirsch, E. M. James, R. James, R. A. James, F. C. Johnson, Vivian K. Jones, T. Kavanagh, K. Kelly, S. M. Lacey, C. E. Lay, Agnes D. F. Lodhi-Hyder, P. Los, Ann H. Low, Margaret R. McDonald, H. R. Marker, L. T. Martin, J. D. Meehan, R. S. Miller, Patricia E. Mortimer, Lilias M. A. Munro, A. I. C. Napier, C. G. H. Newman, J. Nickson, Norma H. W. Noakes, Jean M. North, J. S. Ogilvie, Elizabeth S. Ordish, Pamela M. Ordish, C. G. Owen, M. K. Panikkar, Elizabeth M. Phillips, Kathleen M. Pick, D. A. Potts, Rosemary D. Prior, R. D. H. Reddy, P. I. Reed, D. B. Reynolds, S. B. Rosalki, Annette B. Rosenkranz, A. T. Rowe, N. R. Sales, Dorothy Sanderson, J. R. B. Saxby, J. R. Scarr, Jane M. Scott-Brown, Muriel J. Seaman, E. Silverstone, S. E. J. Smith, J. T. Smyth, J. D. Spouge, T. B. Stephen, J. W. Stephenson, J. C. Stewart, N. D. V. Swallow, Gweneth I. Taylor, Patricia I. Thomas, Diana J. Thuell, A. H. Tooley, S. H. Triay, A. H. Vaughan, H. J. S. Waldeck, N. D. Walker, P. J. C. Walker, T. H. M. Warburton, D. Wardale, P. D. Wardle, R. K. Waterhouse, G. C. Watmough, H. P. Watson, Margaret P. Watson, Joy E. West, V. B. Whittaker, Margaret S. I. Williams, R. S. Williams, T. C. G. Williams, Shelagh R. Wimhurst, C. Wright, D. E. Wright.

Diplomas were granted, jointly with the Royal College of Surgeons of England, to the following successful candidates:

DIPLOMA IN CHILD HEALTH.—June P. Arnold, P. Azzopardi, R. G. Ball, D. M. G. Beasley, B. Bevan, Helen K. Borg, B. D. Bower, Mary C. Buchanan, Vasavi P. Chand, Noeline Clemens, B. Cohen, Subrahmanyam Damayanti, Pamela A. Davies, S. C. Desai, Stella G. de Silva, Judith E. Dey, Elizabeth P. Duncan,

W. E. B. Edge, J. Edwards, B. Flacks, H. W. A. Forbes, Valerie M. Fox, Mary U. Franklen-Evans, Diana M. Game, Sabitri Ghose, J. W. G. Gibb, Christina C. Glynn, H. Gordon, S. Hoffman, A. M. Jafar, Eleanor M. Jones, Zilla M. Kaye, B. F. Laidler, Margaret A. Lees, Annie D. Lindsay, Marjorie J. Lyon, Violet D. MacDermot, F. A. McDonnell, D. Y. Mackenzie, D. A. MacLeod, Angela B. Manning, E. J. Masters, Althea G. Matthews, Elizabeth L. Millar, Ruth E. Mitchell, L. K. Musoke, Jean M. Naylor, Marianna Newman, C. Parkash, Dorothy A. Percy, H. P. M. Perera, O. A. Prosser, Nansi G. Rees, Joan C. C. Reeves, Ruth V. Robson, A. I. Roith, Thea G. T. Rose, N. J. Rothfield, Barbara J. Salisbury, A. J. Salmon, C. E. P. Samarasinghe, N. K. Sarkar, Kathleen J. C. Shaw, Jean McI. Smellie, June M. Smith, Elizabeth J. Sutton, Elizabeth M. Sweet, H. M. Thomas, Shirley L. Tonkin, P. A. Vardy, Barbara J. Walker, Joan Walker, Josephine P. Werren, Patricia L. Wheatley, Phoebe M. White, I. H. Wood, B. Zilberg.

DIPLOMA IN INDUSTRIAL HEALTH.—P. H. Nash.

DIPLOMA IN LARYNGOLOGY AND OTOLOGY.—P. J. Damato.

DIPLOMA IN MEDICAL RADIOTHERAPY.—R. Finney.

DIPLOMA IN OPHTHALMOLOGY.—Judith MacA. Brown, R. U. Chowdhary, K. J. Dastur, J. M. Heaton, S. Itchhaporia, B. R. Jones, Mary A. C. Jones, A. T. Karsgaard, M. K. Mehra, J. Moss, M. Nawaz, C. I. Phillips, A. Samad, J. Singh, J. R. van der Merwe, Billie I. Williams, T. Wilson.

DIPLOMA IN PHYSICAL MEDICINE.—L. S. Bain, E. E. Bullock, A. B. Coyer, J. A. M. Joyce, S. Mattingly, A. P. H. Randle, Dorothy J. Roth, R. A. Shaddick, G. O. Storey.

DIPLOMA IN TROPICAL MEDICINE AND HYGIENE.—I. Ahmad, Anwar-ul-Islam, T. Awuku-Asabre, A. R. O. Bakare, S. A. Biggart, E. B. Bright, G. H. Burgess, C. Cachia, J. E. Cranswick, R. A. Davis, S. R. A. Dodu, P. F. Doherty, I. M. Grant, C. H. Gurd, S. M. M. Haque, H. G. Hendow, C. S. Heymann, Jasmine R. Jacob, V. V. Kalbian, W. N. Laing, A. R. T. Lundie, A. D. A. Maconochie, D. E. Marmion, S. Nadesan, M. C. Peterside, Irene Rajaratnam, D. Ramadwar, S. Paul, A. W. Senft, P. Sirivorasarn, H. G. Skinner, G. J. Stott, Gladys M. Vanniasingham, A. V. A. Vethanayagam, S. Vyas, M. C. Williams, W. Williams, I. H. T. Wilson, R. Woodward.

ROYAL COLLEGE OF OBSTETRICIANS AND GYNAECOLOGISTS

The following candidates have been awarded the Diploma in Obstetrics: J. F. Adams, D. B. Allsop, Avice M. Atkinson, E. Azzopardi, A. L. Baccarini, C. L. Baker, D. Banerjee, S. Basu, G. B. Batchelor, C. H. Bearblock, G. Bheek, R. G. Blair, E. R. Blay, J. F. Boyle, Christine A. Bratt, B. I. Brest, A. R. Brighten, B. St. J. Brown, Sheena M. Buchanan, J. A. B. Burn, Evelyn M. Camrass, G. W. Cardno, C. R. K. Carroll, R. L. Carson, P. C. Chaudhury, N. V. Chivers, Mary J. Clifford, Jean K. M. Clift, Pauline V. Coetsee, Eithne M. Conlon, Gladys Connor, M. R. Coster, P. W. Dagger, Ilid M. L. Davies, R. McN. Dean, C. Dexter, A. N. Dhole, Jeannette Diamond, P. L. C. Diggory, Jean A. Drinkwater, F. G. Elvins, Y. A. Eraj, D. V. I. Fairweather, Patricia D. Fletcher, T. A. Forster, Margaret Fyfe, S. Ghosh, E. O. Gibson, M. C. Gill-Carey, I. R. Gilmore, Agnes M. Glen-Bott, Elsie M. Glennie, Winifred J. A. Graham, A. J. Gray, Mary E. S. Gray, D. Greenbaum, J. F. Grehan, J. V. Groundes-Peace, M. H. Hambling, A. S. Harris, Margaret T. Harvey, J. B. Hickling, N. Ll. Higgins, C. H. Hodge, T. Horner, R. J. Howat, Beryl O. Howie, Penelope C. Humphries, Elsie S. Jaikaran, S. J. Jayawant, Margaret E. Johnson, E. E. Jones, J. Kirloskar, T. Kapadia, B. Keane, Mea W. Kelso, P. McC. Kinloch, A. G. Laing, Irene Leeser, R. S. Lindsay, P. W. Lumley, T. F. Lynch, W. J. Lyness, Bridie O. Lyons, J. D. C. Lyons, K. M. McFadyean, C. N. McFarlane, J. R. McGregor, Anne E. C. MacKinnon, M. L. McMillan, G. R. MacPherson, Frances M. McQuitty, R. I. Maitland, H. Makowska, W. W. Marshall, V. T. Mason, J. E. Mohotti, R. Moncrieff, Ann G. Morgan, W. H. Mortiboys, Winifred A. Morton, E. I. Mulholland, H. H. Neifeld, R. G. Nicholson, T. M. O'Brien, O. K. Ogan, M. S. O'Grady, Gweneth L. O'Reilly, D. R. M. P. B. O'Sullivan, W. J. O'Sullivan, Sheila J. Parker, N. L. Paros, J. E. Phillips, H. O. Phillipson, D. G. Price, I. M. Quest, Dorothy H. E. Ramsay, R. H. Reynolds, J. A. Riedel, J. L. Robertson, Jean M. N. Robotham, A. K. Ray, J. L. Russell, Z. R. Salib, Mary McL. Sayers, F. A. M. El Shazly, Elizabeth C. Shore, S. C. Simmons, J. N. Sircar, G. F. Smith, J. G. Smith, Margaret C. Smith, Margaret I. A. Smith, D. J. Stephens, R. E. Stewart, Elizabeth L. T. Stoddart, Vera Taylor, E. T. Tewson, A. C. Trevan, W. M. E. Tweed, Mary Uprichard, R. J. Venn, A. F. Verney, Anna M. Walsh, Jean M. Webb, C. P. Wendell-Smith, Dorothy M. A. White, C. R. Whitfield, D. K. Williams, G. Williams, A. R. Wilson, C. G. Wilson, J. T. Woodall, E. H. Wyatt.

INFECTIOUS DISEASES AND VITAL STATISTICS

Summary for British Isles for week ending **April 25** (No. 16) and corresponding week 1952.

Figures of *cases* are for the countries shown and London administrative county Figures of *deaths* and *births* are for the 160 great towns in England and Wales (London included), London administrative county, the 17 principal towns in Scotland, the 10 principal towns in Northern Ireland, and the 14 principal towns in Eire.

A blank space denotes disease not notifiable or no return available.

The table is based on information supplied by the Registrars-General of England and Wales, Scotland, N. Ireland, and Eire, the Ministry of Health and Local Government of N. Ireland, and the Department of Health of Eire.

CASES in Countries and London	1953					1952				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	25	0	5	0		32	1	5	0	
Dysentery	419	53	67	8		327	4	57	1	
Encephalitis, acute	6	0	0	0		8	0	0	0	
Enteric fever:										
Typhoid	2	0	2	0	1	2	0	0	0	2
Paratyphoid	8	1	1(B)	0		9	0	1(B)	0	
Food-poisoning	88	12		0		64	6		0	
Infective enteritis or diarrhoea under 2 years				13	18				10	14
Measles*	13,731	629	568	243	168	6,774	294	404	267	484
Meningococcal infection	44	5	25	5	1	48	2	28	2	4
Ophthalmia neonatorum	30	1	4	1	1	44	1	12	0	
Pneumonia†	681	35	223	20	8	820	49	305	10	7
Poliomyelitis, acute:										
Paralytic	34	8	2	0	1	15	1	1	2	
Non-paralytic	7	0				8	1			
Puerperal fever§	220	33	21	1		279	44	15	1	
Scarlet fever	1,047	63	165	35	83	1,043	73	178	14	40
Tuberculosis:										
Respiratory			163	27				182	32	
Non-respiratory			28	7				28	4	
Whooping-cough	3,206	237	429	41	149	2,800	111	168	101	64

DEATHS in Great Towns	1953					1952				
	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire	Eng. & Wales	Lond.	Scot.	N. Ire.	Eire
Diphtheria	0	0	0		0	1	0		0	0
Dysentery	0	0				0	0		0	
Encephalitis, acute		0			0		0			0
Enteric fever	0	0	0			0	0		0	
Infective enteritis or diarrhoea under 2 years	11	0	1	3	0	18		4	0	1
Influenza	23	2	2	0	2	37	4	7	0	1
Measles		0	1		0		0	2	0	2
Meningococcal infection		1	1				1			
Pneumonia	213	38	22	12	6	264	49		18	10
Poliomyelitis, acute	2	1			0	1	0			0
Scarlet fever		0	0		0		0		0	0
Tuberculosis:										
Respiratory	113	17	14	0	11	167	23	14	8	6
Non-respiratory		3	2	0	3		1	2	0	1
Whooping-cough	1	0	0	0	0	1	0		0	0
Deaths 0–1 year	239	30	30	10	20	284	32	39	5	16
Deaths (excluding stillbirths)	5,273	758	606	132	201	5,727	844	643	130	173
LIVE BIRTHS	7,874	1172	971	272	407	7,920	1171	1026	210	472
STILLBIRTHS	217	30	25			211	20	23		

* Measles not notifiable in Scotland, whence returns are approximate.
† Includes primary and influenzal pneumonia.
§ Includes puerperal pyrexia.

Vital Statistics

Smallpox in the North Country

Up to noon, May 12, 30 cases had been reported, including 7 deaths. 3 new cases have been reported since last week. These are :—*Baildon U.D.:* Male aged 19, vaccinated for the first time on May 5, the rash having appeared on May 4. *Leeds C.B.:* Female aged 18, daughter of another case, vaccinated for the first time on May 2 ; rash appeared on May 8. Male aged 16, brother of the previous case, vaccinated for the first time on May 2 ; disease became evident on May 10.

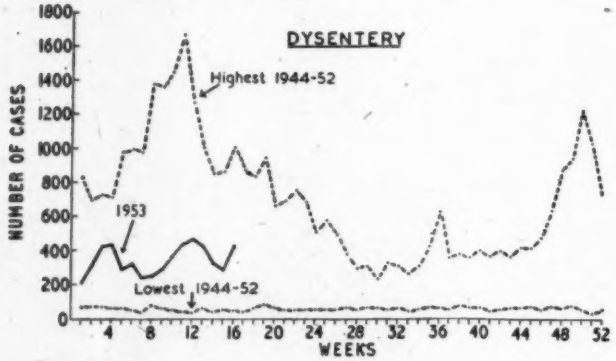
A feature of the epidemic is that a number of cases have been desperately ill so early in the course of the illness that diagnosis has been made difficult or impossible at this critical stage owing to the absence of distinguishing signs or symptoms. There have also been patients exceedingly ill in the early stages who have subsequently had sparse rashes difficult to identify. The cause of death of 2 was not diagnosed until after death. Medical or surgical emergencies have at first been suspected in some cases, the diagnoses ranging from uraemia to acute abdomen requiring laparotomy.

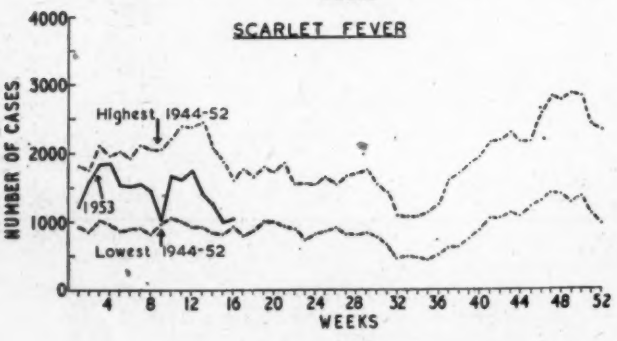
Industrial Accidents and Disease

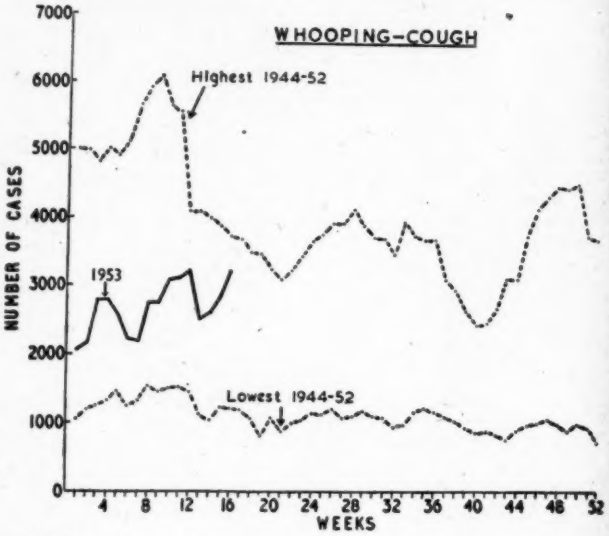
The number of workpeople (other than seamen) in the United Kingdom whose deaths from accidents in the course of their employment were recorded in March was 124, compared with 121 in the previous month and 132 in March, 1952. The number of cases of industrial disease reported was 49, including 4 from lead poisoning, 22 from epitheliomatous ulceration, and 23 from chrome ulceration. There were 3 deaths—from epitheliomatous ulceration.—*Ministry of Labour Gazette,* April, 1953.

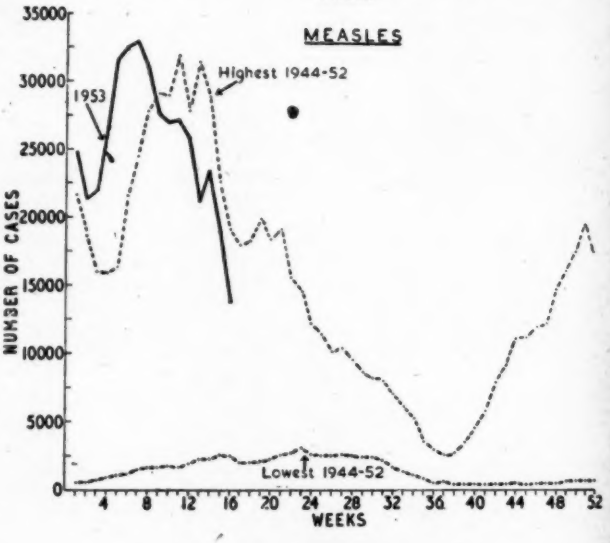
Graphs of Infectious Diseases

The graphs below show the uncorrected numbers of cases of certain diseases notified weekly in England and Wales. Highest and lowest figures reported in each week during the nine years 1944–52 are shown thus - - - - - - -, the figures for 1953 thus ————. Except for the curves showing notifications in 1953, the graphs were prepared at the Department of Medical Statistics and Epidemiology, London School of Hygiene and Tropical Medicine.









Infectious Diseases

The chief feature of the returns of infectious diseases in England and Wales during the week ending April 25 was a decrease of 5,130 in the number of notifications of measles, from 18,861 to 13,731. The increases in incidence were 359 for whooping-cough, from 2,847 to 3,206 ; 137 for dysentery, from 282 to 419 ; and 53 for scarlet fever, from 994 to 1,047.

The largest declines in the number of notifications of measles were 502 in Lancashire, from 1,832 to 1,330 ; 429 in Surrey, from 1,165 to 736 ; 283 in Staffordshire, from 858 to 575 ; 230 in Kent, from 628 to 398 ; 224 in Essex, from 703 to 479 ; 215 in Devonshire, from 628 to 413 ; 206 in London, from 835 to 629 ; and 205 in Gloucestershire, from 877 to 672. The largest rises in the incidence of whooping-cough were 87 in Yorkshire West Riding, from 165 to 252 ; and 56 in London, from 181 to 237 ; and the largest falls were 64 in Cheshire, from 141 to 77 ; and 59 in Lancashire, from 556 to 497. Only small variations were recorded in the local returns of scarlet fever. The number of notifications of diphtheria was 7 more than in the preceding week, but no large fluctuations were recorded in the local returns.

41 cases of acute poliomyelitis were notified during the week. These were 8 more for paralytic and 1 fewer for non-paralytic cases than in the preceding week. The largest returns were London 8 (Fulham 3), Middlesex 5 (Willesden M.B. 2), Essex 4, and Kent 4.

The largest centres of dysentery were Lancashire 93 (Liverpool C.B. 26, Manchester C.B. 23, Preston C.B. 21), Leicestershire 59 (Leicester C.B. 59), London 53 (Islington 9

and the remaining cases spread over 18 boroughs), Middlesex 44 (Edmonton M.B. 31), Yorkshire North Riding 33 (Middlesbrough C.B. 33), and Essex 17.

Quarterly Returns for Eire

During the December quarter of 1952 the birth rate was 20.0 per 1,000 of the population, and was 1.3 above the rate for the fourth quarter of 1951. The infant mortality rate was 40 per 1,000 registered births, and was 1 below the rate for the corresponding quarter of 1951. The general death rate was 11.5 per 1,000 of the population and was 0.8 above the rate for the December quarter of 1951.

For the whole year the birth rate was 21.8 per 1,000, and was 0.6 above the rate for 1951. The infant mortality was 41 per 1,000 registered births. This was the lowest annual rate ever recorded in Eire, being 4 below the previous lowest level recorded in 1951 and 1950. The death rate from all causes was 11.9 per 1,000. This was the lowest in recent years, being 2.4 below the rate for 1951.

There were 1,229 deaths from respiratory tuberculosis, and 366 from other forms of tuberculosis. These deaths were 962 and 238, respectively, below the average of the five preceding years. Deaths from infectious diseases included 230 from influenza, 166 from gastro-enteritis, 88 from whooping-cough, 45 from measles, 16 from acute poliomyelitis, 10 from scarlet fever, and 7 from diphtheria.

Week Ending May 2

The notifications of infectious diseases in England and Wales during the week included scarlet fever, 1,139, whooping-cough 3,373, diphtheria 13, measles 10,752, acute poliomyelitis 29, dysentery 466, paratyphoid fever 6.

Medical News

Sixth World Health Assembly.—On May 11 the sixth World Health Assembly, which is meeting in Geneva, appointed Dr. Marcolino Candau (Brazil) Director-General of W.H.O. in the place of Dr. Brock Chisholm, who retires in July (see *Journal*, February 7, p. 345). The voting was 47 to 16. The Assembly opened on May 5 under the chairmanship of the outgoing president, Dr. Juan Salcedo (Philippines), and proceeded to elect Dr. Murched Khater, Minister of Health of the Syrian Republic, as president. Dr. Melville Mackenzie (Ministry of Health, London) was chosen as one of the three vice-presidents. During the Assembly technical discussions are being held on the most effective and the cheapest ways of combating tuberculosis, syphilis, and typhoid.

Moyne Institute of Preventive Medicine.—On May 7 the Marchioness of Normanby opened the Moyne Institute of Preventive Medicine in Dublin. She has given the Institute, which is in the grounds of Trinity College, as a memorial of her father, the first Lord Moyne, who was assassinated in Cairo in 1944. The Institute will house the School of Bacteriology under Professor F. S. Stewart, the late Professor Joseph Bigger's successor, and a new School of Social Medicine under Professor W. J. E. Jessop, the honorary secretary of the Irish Medical Research Council. The School of Social Medicine is the first of its kind in Eire: undergraduate teaching there will include courses in hygiene, nutrition, public health administration, and industrial medicine, the last being a new departure; postgraduates will be trained for the diploma in public health.

Society of Chiropodists.—The annual dinner of the Society of Chiropodists was held at the Park Lane Hotel on May 7 with the president, Mr. John Hanby, F.Ch.S., in the chair. In proposing the health of the society Sir Henry Souttar said it was about 20 years ago that the B.M.A. thought it was time to recognize officially the work done by medical auxiliaries, and the Board of Registration of Medical Auxiliaries was formed. Important among the auxiliaries were the chiropodists. "You," he said to the assembled company, "are the most important body of the whole group." In response Mr. John Hanby said that the society had been built up on three things: their educational programme, ethical conduct with regard to its members, and close association with the medical profession. He paid a special tribute to Mr. Norman C. Lake, who had been their first medical representative on the Board of Registration. Mr. Hanby said that some 70% of the adult population of this country had some form of foot disability. The first item in their programme was the prevention of such disability, and this they hoped to do by attending to the feet of schoolchildren. Another important problem they were faced with was the alleviation of the painful feet which were so often the plight of the aged poor. The chiropodists wanted something more than a voluntary register: they wanted a State register so that the public would be able to distinguish the qualified from the unqualified. The toast of the guests was proposed by Mr. S. Coates, F.Ch.S., vice-president of the society, and in response Sir Zachary Cope said he thought the training course for chiropodists was better than that for any other group of medical auxiliaries. He supported Mr. Hanby's views in favour of a State register, and had some critical observations to make on the action, or lack of action, on the part of the Minister of Health on the recommendations made by the committee of which Sir Zachary had been chairman.

Buckston Browne and Gray Hill Dinner.—The Buckston Browne and Gray Hill dinner of the Harveian Society of London was held at the Royal College of Surgeons on May 6, with the president, Dr. Tom Hare, in the chair. In proposing the health of the society the Very Reverend C. C. Thicknesse, the Dean of St. Albans, said that Harvey had died in a time of tragedy, and had died a sorrowful man because he never saw the fruits of his labours. We should, he remarked, do well to stick to our traditions, for custom outlived rule. It was therefore well worth while keeping such a society in health, and he wished it prosperity. In a speech full of pleasant reminiscence, Dr. Tom Hare in response referred felicitously to the benefactors, the late Sir Buckston Browne and the late Sir Norman Gray Hill. Sir Buckston had been a great benefactor of the medical profession, and to him they owed the foundation of the annual prize essay of the society. Dr. D. A. Imrie, one of the honorary secretaries of the society, enlivened the traditional toast of the guests by many Scottish stories told with a richly appropriate accent. The response to this toast was made by Mr. Justice Danckwerts, who reminded the diners that one of Harvey's patients was Francis Bacon. Dr. G. F. Abercrombie, also replying for the guests, said that this was the first invitation which had been officially extended to the new College of General Practitioners, of whose foundation council he is chairman.

Royal Dental Hospital of London.—About 300 past students and visitors attended the 36th annual clinical "At Home" at the Royal Dental Hospital on May 9. Of the demonstrations on view in the Conservation Department the most ambitious was one entitled "The Restoration of the Partially Edentulous Mouth," by members of the junior teaching staff. In the Prosthetics Department the demonstrations included "Impression Techniques and Materials," "Immediate Replacement," "Balanced Articulation in Full Dentures," and "Bite Rehabilitation." Clinical demonstrations, including gingivectomy and electro-surgery for gingivoplasty, were given by members of the Department of Periodontology. In addition there were operations under both local and general anaesthesia to be seen, an exhibition of pathological specimens, and demonstrations of modern techniques in intra-oral photography and post-operative speech therapy. In the afternoon clinical cases were shown and there was a "Brains Trust." The dinner in the evening at Claridge's was presided over by Mr. F. R. Moser, an old student and benefactor of the school.

Opening for Medical Editor.—In this week's advertisement columns the Canadian Medical Association invites

applications for the position of Editor of the *Canadian Medical Association Journal*. They seek applications from medical graduates, preferably under the age of 45, and offer a salary of 10,000 dollars a year or more, according to qualifications and experience. The *Canadian Medical Association Journal* is published monthly and stands high in reputation among the medical periodicals published in different parts of the world. The post would appear to offer a most attractive opportunity for any doctor with the necessary experience.

Missing Harveian Oration.—The library of the Royal College of Physicians has now been able to complete its set of published Harveian Orations (see *Journal*, April 18, p. 893). The President of the Royal College of Surgeons has presented his College's copy to the library.

Royal College of Physicians of Edinburgh.—At an extraordinary meeting of the Royal College of Physicians of Edinburgh, held on May 5, the President, Dr. W. A. Alexander, announced that Queen Elizabeth the Queen Mother had graciously signified her acceptance of the Honorary Fellowship of the College.

Sir John Stopford, F.R.S., vice-chancellor and professor of experimental neurology at Manchester University, received the honorary degree of LL.D. at the jubilee celebrations of Liverpool University last week.

Professor C. A. Wells, professor of surgery at Liverpool University, has been lecturing this week in Syria on behalf of the British Council. He is on his way to the University of Hong Kong, where he will act as external examiner.

COMING EVENTS

Royal Medical Benevolent Fund.—The annual general meeting will be held on Tuesday, June 9, at the Medical Society of London, 11, Chandos Street, W.1, at 5 p.m. Lord Webb-Johnson will be in the chair.

Polish Medical Association.—The annual meeting of the Polish Medical Association will be held on May 23 and 24 at the White Eagle Club, 2, Albert Gate, Knightsbridge, S.W.1. On May 23 there will be a meeting at 3 p.m. and a party at 9 p.m., and on May 24 there will be lectures at 10 a.m. and 3 p.m., followed by a social gathering of former students of the Polish School of Medicine in Edinburgh at 4 p.m. Those wishing for further information should communicate with the hon. secretary, Polish Medical Association, 14, Collingham Gardens, London, S.W.5.

Rodent Control Exhibition.—The Royal Sanitary Institute, in collaboration with the Infestation Control Division of the Ministry of Agriculture and Fisheries, is staging an exhibition on rodent control at the Museum of Hygiene of the Institute, 90, Buckingham Palace Road, London, S.W.1, from May 26 to June 20. The exhibition, admission to which will be free without ticket, will be open from 10 a.m. to 5 p.m. on weekdays, and 10 a.m. to 12 noon on Saturdays.

Rabelais Festival in France.—A festival to mark the fourth centenary of the death of François Rabelais is to be held in Angers, France, from June 6 to 9 inclusive. There will be an official reception to those attending the festival on June 6, and at 8.30 p.m. "gastronomic junketing and enthroning in the order of the Confraternity of the 'Sac à Vins' at the Greniers St. Jean, Angers." On June 7 the party will visit Saumur, where they will see the Angevine vineyard and taste the best productions, and in the evening there is to be a garden party in the Beaux-Arts Gardens at Angers, "followed by a Rabelais evening party." The programme for June 8 includes visits to several places of interest in Touraine, with dinner at the wine cellars of Vouvray. On June 9 the party will visit Poitiers, and the festival will conclude with supper at Touffou Castle and "Curée aux Flambeaux." Those wishing for further information are asked to communicate with Syndicat d'Initiatives, 71, rue Plantagenet, Angers (Maine et Loire).

SOCIETIES AND LECTURES

A fee is charged or a ticket is required for attending lectures marked ●. Applications should be made first to the institution concerned.

Monday, May 18

●POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Professor R. V. Christie: Dyspnoea.
ROYAL EYE HOSPITAL.—5.15 p.m., Mr. L. Mushin: Problem of Sorting Ophthalmic Out-patients.
UNIVERSITY COLLEGE.—At Physiology Theatre, 4.45 p.m., Sir Rudolph Peters, F.R.S.: Inhibitors and Intracellular Chemical Dissection.

Tuesday, May 19

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. S. C. Gold: Lupus Erythematosus.
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE.—5.15 p.m., Newsholme Lecture by Professor Alan Moncrieff: Infant Welfare and the Ministry of Health.
ROYAL EYE HOSPITAL.—5 p.m., Mr. T. M. Tyrrell: Surgery of the Lacrimal Sac.
ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Dr. C G. King (New York): Some Aspects of Nutrition.
SOUTH-WEST LONDON MEDICAL SOCIETY.—At Bolingbroke Hospital, 8.30 p.m., Dr. B. Barling: Diseases of the Thyroid.
WRIGHT-FLEMING INSTITUTE OF MICROBIOLOGY, St. Mary's Hospital Medical School.—5 p.m., Almroth Wright Lecture by Brigadier J. S. K. Boyd, F.R.S.: Bacteriophage Typing and Epidemiology.

Wednesday, May 20

INSTITUTE OF DERMATOLOGY.—5.30 p.m., Dr. J. O. Oliver: Pathology of Lupus Erythematosus.
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE.—5.15 p.m., Newsholme Lecture by Professor Alan Moncrieff: School Health and the Ministry of Education.
MIDDLESEX HOSPITAL.—4.30 p.m., Sanderson-Wells Lecture by Professor E. C. Dodds, F.R.S.: Chemicals and Food, a Reconsideration.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Dr. F. O. MacCallum: Laboratory Diagnosis of Virus Diseases.
ROYAL COLLEGE OF SURGEONS OF EDINBURGH.—3.30 p.m., Dr. R. B. Cattell (Boston): Carcinoma of the Pancreas.
ROYAL COLLEGE OF SURGEONS OF ENGLAND.—6.30 p.m., Film by Professor A. M. Boyd and Surgical Unit of Manchester University: Dextran—The New Narrow Fraction.
ROYAL EYE HOSPITAL.—5.30 p.m., Mr. J. F. P. Deller: Optics of Retinoscopy.

Thursday, May 21

EDINBURGH UNIVERSITY.—At University New Buildings, 5 p.m., Dr. Douglas Guthrie: Trends and Fashions in Medicine.
●HAMPSTEAD GENERAL HOSPITAL.—3 p.m., Dr. W. Gunn: Use and Abuse of Chemotherapy; 4.15 p.m., Mr. E. O. Harris: Modern Trends in E.N.T.
HONEYMAN GILLESPIE LECTURE.—At University New Buildings, Edinburgh, 5 p.m., Dr. M. W. Paterson: Some Abnormalities of the Optic Disk.
LONDON JEWISH HOSPITAL MEDICAL SOCIETY.—At 11, Chandos Street, W., 8.30 p.m., Professor D. Slome: Experimental Surgery.
LONDON SCHOOL OF HYGIENE AND TROPICAL MEDICINE.—5.15 p.m., Newsholme Lecture by Professor Alan Moncrieff: Deprived Child and the Home Office.
NORTH-WESTERN TUBERCULOSIS SOCIETY.—At Manchester Royal Infirmary, 5 p.m., Dr. W. Robinson: Air Cysts of the Lung; Dr. G. Penrhyn Jones: Pulmonary Adenomatosis.
●POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. E. S. Clarke: Cerebral Circulation.
ROYAL SOCIETY OF TROPICAL MEDICINE AND HYGIENE.—7.30 p.m., Dr. J. C. Broom: Leptospirosis in Tropical Countries. A discussion will follow.
ST. ANDREWS UNIVERSITY.—At Physiology Department, Dundee, 5 p.m., Professor H. Scarborough: Purpura.
ST. GEORGE'S HOSPITAL MEDICAL SCHOOL.—5 p.m., Sir Paul Mallinson: postgraduate demonstration in psychiatry.
●SOCIETY FOR ENDOCRINOLOGY.—At Medical Society of London, 9.30 a.m., Symposium: Determination of Adrenal Cortical Steroids and their Metabolites.

Friday, May 22

INSTITUTE OF DERMATOLOGY.—5.30 p.m., clinical demonstration by Dr. W. N. Goldsmith: Xanthoma, Nectobiosis Lipoidica, and Granuloma Annulare.
●INSTITUTE OF OBSTETRICS AND GYNAECOLOGY.—At Queen Charlotte's Hospital, 2 p.m., Dr. J. P. Martin: Neurological Complications in Pregnancy and Puerperium.
POSTGRADUATE MEDICAL SCHOOL OF LONDON.—2 p.m., Mr. F. Masina: Diagnosis and Surgery of Bladder Tumours.
●POSTGRADUATE MEDICAL SCHOOL OF LONDON.—4 p.m., Dr. B. M. Wright: Inhalation and Retention of Aerosol.

BIRTHS, MARRIAGES, AND DEATHS

BIRTHS

Benians.—On April 27, 1953, at Bradford, Yorks, to Edith, wife of Dr. Richard Benians, a daughter.
Duff.—On May 5, 1953, at the Royal Free Hospital, London, W.C., to Audrey (formerly Heaton-Smith), wife of Dr. A. Dewar Duff, 5, Tanza Road, London, N.W., a daughter—Elizabeth Anne.
Gill.—On April 27, 1953, at Godalming, Surrey, to Aileen, wife of W. G. Gill, M.Chir., F.R.C.S., a daughter.
Grey-Turner.—On May 4, 1953, at the Garrett Anderson Maternity Home, Belsize Grove, London, N.W., to Lilias (formerly Tomlinson), wife of Dr. Elston Grey-Turner, a son.
Wright.—On April 29, 1953, at Woodlands Road Hospital, Barry, Glam, to Sheila (formerly Smith), wife of Dr. Martin Wright, a son.

DEATHS

Hodgson.—On March 23, 1953, at The Lindens, Alresford, Hants, Harold Hodgson, M.B., B.S., J.P., aged 86.
Kalra.—On March 22, 1953, at 176, Clapham Road, London, S.W., Atam Parkash Kalra, M.B., B.S., D.P.H., D.C.H., aged 30.

Any Questions?

Correspondents should give their names and addresses (not for publication) and include all relevant details in their questions, which should be typed. We publish here a selection of those questions and answers which seem to be of general interest.

A Chill

Q.—*What is a chill?*

A.—The expression "a chill" used by a patient may mean one of many conditions. It should mean the initial chilliness which is often the first symptom of an illness. It may mean the cold stage which precedes a mild or even a severe rigor, when the skin feels cold, although the rectal temperature is raised. The patient may have been exposed to cold, and, if so, will ascribe the "chill" to this.

The expression is also attached to an organ. Thus "a chill" on the lung may mean anything from bronchitis, pneumonia, or pleurisy to tuberculosis. "A chill" on the kidneys may be an acute nephritis or a pyelitis. "A chill" on the bladder probably means a cystitis, but a careful examination in all these conditions may reveal other causes. "A chill" on the liver is an old name for a peculiar syndrome which shows itself by a chilly feeling, a tendency to hug the fire, great distaste for all foods, especially fatty foods, a very dirty tongue which may taste horrid, and constipation. It is not caused by overeating, which is often supposed to be the case with children, nor is it due to eating food which is bad. There is no evidence that the liver is involved, though it may be. The condition may recur at irregular intervals, once or even twice a year in some people. It is best treated by avoiding all food except very dry toast and meat extracts for 24–48 hours; a brisk purge of calomel should be followed by magnesium sulphate as soon as the calomel begins to act. The attack ceases in 24–48 hours under this treatment, though whether treatment has anything to do with this is another matter.

Sexing the Foetus

Q.—(1) *What is the new American "saliva test" for the predetermination of the foetal sex during pregnancy? How early is it applicable and how accurate is it?* (2) *Are there any reliable tests for this purpose?*

A.—(1) The test was described by G. W. Rapp and G. C. Richardson in *Science* (1952, **115**, 265). On the morning of the test the patient should not clean her teeth with any sort of paste or powder, but should chew a piece of solid paraffin for 20 minutes and discard the resulting flow of saliva. This removes all particles of food. Another piece of paraffin is then chewed and the saliva collected. Foam should be avoided, and 2 ml. of saliva is necessary for the test. To this is added two drops of 0.5N sodium hydroxide solution and then 3 ml. of chloroform. The mixture is shaken vigorously and allowed to stand until the chloroform sinks to the bottom. The supernatant fluid is then removed with a pipette, and to it is added four drops of a saturated solution of dinitrophenylhydrazine in 95% ethyl alcohol. (This reagent must be freshly made each day.) The tube is allowed to stand 15 minutes for the reaction to complete, and then 2 ml. of 0.5N sodium hydroxide is added. Readings must not be taken prior to the addition of the latter. A brown coloration indicates that the foetus is male. If the solution remains colourless or yellow, or if any colour fades within two minutes, a female foetus is predicted.

The basis of the test is the demonstration of free oestrogen in the saliva; it is said that this is present only when the foetus is male. It is no use applying the test until after the 24th week of pregnancy, and it is inaccurate after the 36th week. Drugs such as aspirin, or anything containing the ketone or aldehyde group, give a false positive reaction. So the test is unreliable in the presence of carbohydrate disturbances, and it should not be carried out until all forms of medication have been discontinued for 48 hours.

It is claimed that if all the instructions are followed carefully the test is accurate in 93% of cases, but this has not yet been confirmed and it is too soon to assess its value.

This test, or a close modification of it, is offered to customers at a well-known baby-clothes store in Paris.

(2) There is no other reliable and practical test for the determination of the sex of the unborn child. A few years ago it was shown that, if the excretion products of adrenal hormones in the maternal urine are measured throughout pregnancy, there is a difference in the curve in mid-pregnancy according to the sex of the child. This corresponds to the active phase in the foetal adrenal of male foetuses at that time. This may well be the case, but the method requires repeated accurate and complicated chemical assays and is extremely difficult to apply—so much so that its reliability has never been put seriously to test.

Flies in the Kitchen

Q.—*What is the best insecticide for keeping kitchens, canteens, and lavatories free of flies? How should it be applied, in what concentration, and how often?*

A.—At present the synthetic residual insecticides D.D.T. (dichlor-diphenyl-trichlorethane) and *gamma* benzene hexachloride ("gammexane") are the most satisfactory substances for the persistent control of the house-fly in Britain. The methods of using these materials as residual sprays have been described several times in the last six years: full details are given in an article on "Control of House-flies" (*Monthly Bull. Minist. Hlth, Lond.*, 1945, **4**, 147) and further information in another article on "Insect Pests of Catering Establishments" (Ibid., 1950, **9**, 68). Unfortunately, in many parts of the world where these insecticides have been used in houses more extensively than in Britain, races of house-flies appear which are highly resistant to them. When this happens these synthetic insecticides are practically useless for controlling flies; and this may ultimately happen in Britain. The only alternatives then are to fall back on methods in use before the advent of D.D.T. These include: careful and regular disposal of garbage, screening, fly-papers, pyrethrum fly-sprays (which are effective but without residual action), and poison baits. A good, safe poison bait can be made by adding 1% of formaldehyde to milk and water containing a little sugar. A little is added daily to saucers containing pads of cotton-wool or blotting-paper.

Diffuse Otitis Externa

Q.—*What can be done to prevent recurrent diffuse otitis externa in which the ear passage swells up and may become occluded? There is great pain, but no pus is present.*

A.—Diffuse otitis externa often requires treatment over a long period to make it subside and to prevent a recurrence. In most cases it will be found that the older remedies are the most effective. Any debris in the external meatus must first be removed, preferably by careful and gentle mopping under direct vision. Then the ear canal should be filled with 1/2,000 lot. hydrarg. perchlor. in normal saline which has been warmed to body temperature. After two minutes the lotion should be drained out, and then three drops made of 1 drachm (4 g.) of dilute mercuric nitrate ointment (*N.F.*) in 1 oz. (28.4 ml.) of expressed almond oil (*B.P.*) should be instilled. The drops should be warmed to body temperature. During the actual treatment the head should be on one side resting on a table or pillow with the affected ear uppermost. After the treatment it is a wise precaution to keep a piece of wool in the ear for a short period to absorb any of the surplus fluid which may drain away.

In the acute stage, and particularly if there is much swelling and pain, a wick of wool or gauze may be left in the ear for 24 hours, and a solution of one part *meta*cresyl acetate ("cresatin") to three parts of the oily mercurial drops mentioned above may be used to soak the wick in and also to drop into the ear on top of the wick every four hours. A 3% solution of aluminium acetate instead of the oily drops often helps to reduce the swelling. The infecting organism will often be found to be Gram-negative, and as a rule the most effective antibiotic is choramphenicol by mouth. The local application of chloramphenicol or polymyxin is successful in some cases, but as it is sometimes irritating it is probably better to avoid such application in acute cases.

Recurrent otitis externa may sometimes be associated with dandruff, and in such cases a scalp lotion containing mercury and salicylic acid and sulphur will be helpful. Patients with obstinate external otitis should be advised to avoid at all costs getting water into their ears. Although otitis externa may not be accompanied by any obvious discharge, it will often be found that there is debris in the ear canal, particularly in its deeper and more inaccessible part, and until this debris has been thoroughly cleared out the inflammation is unlikely to subside.

Potatoes and Sulphur Dioxide

Q.—*Some cooks soak peeled potatoes overnight in water to every gallon (4.5 litres) of which they add 1 tablespoonful (14 ml.) of a preparation containing approximately 9% of sulphur dioxide. What is the object in doing this, and is the practice harmful?*

A.—Preparations containing sulphur dioxide, in chemically combined form, act as strong reducing agents. They have proved very effective for preserving fruits and vegetables both in domestic bottling and in manufacturing processes. Presumably they are added to the water covering peeled potatoes in order to prevent blackening, which otherwise may tend to occur through the oxidation of tyrosine to melanin by an enzyme liberated from the damaged tissues. The sulphur dioxide also protects vitamin C. There is no evidence that it is harmful in the amounts which are used.

Low-protein Diets and High Fertility

Q.—*I understand that J. R. Slonaker showed that rats fed on diets containing very little protein had particularly large and numerous litters. Has this work been confirmed? Is there any reason to believe that a similar effect may occur in man?*

A.—In speaking of "particularly large and numerous litters" the questioner is under a misapprehension about normal reproduction in the rat. The laboratory rat has an average litter size of 7 to 8 young, and very large litters of 15 or 16 young are not uncommon in most strains, the largest litter size at birth recorded for the Wistar colony of albino rats being 18. In the experiments recorded by Slonaker on the effect of different proportions of protein in the diet of rats, the largest average litter size reported was 5.7 young. This is clearly well below the average for a normal healthy stock receiving an adequate diet. The diet contained 14% protein.

In the preparation of the diets having different protein contents the increased protein was obtained in Slonaker's experiments by the addition of increasing amounts of meat scrap to a basal mixture of constant formula, thus progressively diluting it. At the highest level (26% protein) about 50 g. meat scrap was added to every 100 g. basal mixture. Even a "rich" diet would be unlikely to withstand such dilution without the risk of becoming deficient in some essential factor not present in meat scrap. Moreover, the basal diet used by Slonaker was not adequate. Apart from the poor reproduction at all protein levels the females lost weight during lactation, which does not occur if the diet is adequate.

The small litter size obtained with the higher levels of protein in Slonaker's diets is likely to be the result of a deficiency in the diet and not of the level of protein. The work has not been confirmed. On the contrary, better reproduction in rats on a diet containing 40% protein than on diets containing 25% or 15% protein has been reported by McCoy (*J. Biol. Chem.*, 1940, **133**, lxiv). In this work the concentration of vitamins, minerals, and fats was kept constant, and the added protein replaced dextrin in the diet.

It is well known that fertility in man is not dependent on a high nutritional level.

Recurrent Urinary Symptoms after Coitus

Q.—*What are the likely causes of recurrent attacks of cystitis (frequency of micturition and dysuria) in a woman following coitus? Dyspareunia, due apparently to vaginismus, has resulted in coitus being infrequent. Full investigation of the urinary tract has proved negative, but on one occasion after discharge from hospital a profuse growth of Bact. coli was obtained from the urine. The condition dates from after the birth of the patient's first child.*

A.—Since the investigations of the urinary tract gave negative results the diagnosis of cystitis must be put in doubt. The occasional finding of *Bact. coli* in the urine is of little significance unless pus is present as well. Attention might next be directed to the urethra itself and to that part of the vaginal wall immediately around the external meatus. Is there any sign of chronic urethritis with a nidus of infection in Skene's tubules? A more likely finding, however, is a periurethritis which is part of a chronic trichomonal or monilial vaginitis. This can cause symptoms such as those described, and without producing much discharge and pruritus. Moreover, such a condition is not only made worse by coitus but might itself be the cause of the dyspareunia. Careful and repeated examinations of vaginal swabs may be necessary to confirm this diagnosis.

Other possible explanations of the symptoms which come to mind are: (1) Bruising of the urethra during coitus arising as the result of vaginismus, which makes penetration difficult and thrusts the male organ forwards on to the urethra. (2) A urethral reaction to chemicals used as a contraceptive—even to a rubber condom. (3) A defence mechanism in order to avoid coitus for some underlying reason such as fear of pregnancy.

Treatment depends on finding the cause of the trouble.

Corrections.—In the article on "Toxoplasmosis in Relation to Mental Deficiency" (March 28, p. 702) reference was made to the incidence of positive reactions to the Schick test rising with increasing age. The authors of the article write to say that the reference should have been to negative reactions, since in the case of diphtheria, unlike tuberculosis and toxoplasmosis, previous contact with infection results in a negative skin reaction.

In the report of the Extraordinary General Meeting (*Supplement*, May 9, p. 206) "Mr. F. S. Gould (Birmingham)" should have read "Dr. F. E. Gould (Birmingham)." The error is regretted.

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